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In The Beginning

And God said, Let the earth bring forth grass, the herb yielding seed, and the fruit tree yielding fruit after his kind, whose seed is in itself, upon the earth: and it was so. And the earth brought forth grass, and herb yielding seed after his kind, and the tree yielding fruit, whose seed was in itself, after his kind: and God saw that it was good. And the evening and the morning were the third day. (Gen. 1:11-13)

AN ESSAY ON ONIONS

And God said Let the earth bring forth Allium, and the earth brought forth Allium, and God saw that it was good. The genus by one account was given by the Gods for the use and benefit of man, to please the eye and gladden the heart; for taste and for smell, to strengthen the body and to enliven the soul. According to another account the genus was brought to Adam, the first man, by messengers from another world in the days when the Gods planted a garden eastward in Eden. Perhaps the genus was known and used by the sons of God in the days of Noah when there were giants in the earth; perhaps later spread to distant corners of the earth after the flood.

There is no doubt that the virtues of the genus Allium were known to early man. Members of the genus appear in the art and records of the ancient Egyptians, dating perhaps as early as Abraham the seer. The genus was certainly known to the children of Israel, for they complained against Moses the prophet when he led them out of their land of leeks, onions, garlic and cucumbers. Healing powers of the genus were also greatly appreciated and much used by the ancient herbalists and alchemical healers. Many of these uses have been preserved and passed down through the ages from generation to generation. Although the educated and intellectual of our time still appreciate the gastronomical delights of Allium, they smile at its continued use in folk medicine.

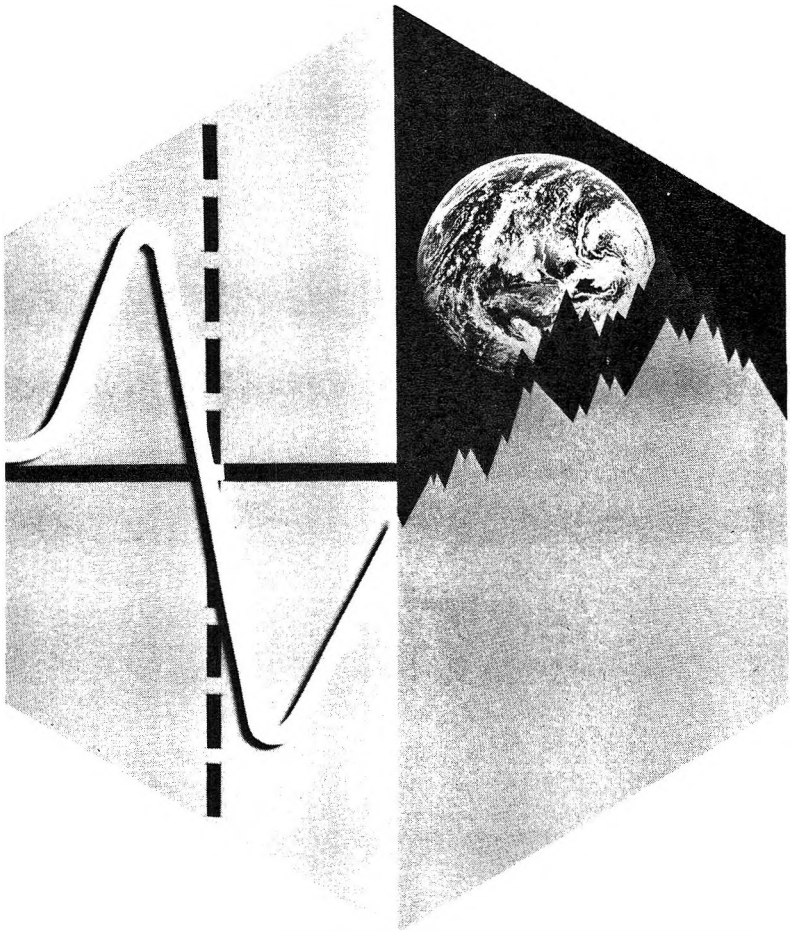
Modern investigators in addition to an appreciation of the gustacatory and olfactory properties of Allium have discovered that extracts of the genus also posses antibacterial, antifungal, antitumor, larvicidal, insecticidal and insect repellant properties. The activity is due at least in part to the presence of sulfinic acid derivatives, particularly the thiosulfinate esters which are also responsible for the odor and taste. Hydrolysis of these esters gives rise to the odorous mercaptans, sulfides and disulfides which are also present in the genus. It is probably only a matter of time until allylsulfinic acid and the lower aklyl sulfinic acids, also products of thiosulfinate hydrolysis, are shown to be present in Allium. Cauliflower, another odorous sulfur rich vegetable, has already been shown to contain methane sulfinic acid which is required as a co-factor in the enzyme catalyzed formation of ethylene from the amino acid methionine via methional. We cannot help but wonder about the importance of sulfinic acids and their derivatives in other sulfur rich plants such as broccoli, cabbage, kale, turnips, radish, mustard, watercress and horseradish.

Another sulfinic acid, 2-aminoethane sulfinic acid, is present in rat brain (0.5%) and the mollusc, Septifer virgatus. This acid is also isolated in the degradation products of icthiamin during structural elucidation and is known to be an intermediate in the *in vivo* oxidation of cysteine. Perhaps sulfinic acids and their derivatives are also important in man, perhaps even necessary to "strengthen the body." We wonder what contribution Allium has made to the well being of man down through the ages. We can only wonder how much the ancients knew about the sulfinic acids of Allium. Perhaps this knowledge was part of the ancient revelation. How much has been lost with the passing of time!

Sulfinic acids and their derivatives may well turn out to be as ubiquitous and necessary to life as the more familiar carboxylic acids and their derivatives. Methane sulfinic acid is an analog of acetic acid, hydroxymethane sulfinic acid, an analog of glycolic acid, and aminomethane sulfinic acid, an analog of glycine. 2-Aminoethane sulfinic acid is an analog of the amino acid β-alanine as well as the biologically important sulfonic acid taurine. Benzene sulfinic acid is an analog of benzoic acid. Who knows at what level or in what organism sulfinic acids may next be found to be of importance. Perhaps sulfinic acids are important in one-carbon transfers at the level of methanol or formaldehyde, perhaps in the natural formation of methane or methly mercaptan, perhaps in the natural ripening process, perhaps as radical initiators or carriers in the electron transport process. We can only guess.

Contemporary man in addition to making gastronomic use of sulfinic acid derivitives in Allium, also makes use of other sulfinic acids for a wide variety of purposes such as snythetic intermediates; reducing agents; dye brighteners, stabilizers, fixers, and couplers; copolymer solution stabilizers; acrylate adhesive curing catalysts; blowing agent activators; rubber vulcanizers; detergents; and tanning agents. For your convenience we have listed below a few of the sulfinic acids now available from Parish. Perhaps one of the sulfinic acid sodium salts is a flavor inhancer, the monosodium glutamate of the future, perhaps another salt promotes wound healing, maybe even a cure for cancer. Maybe you ought to be thinking about sulfinic acids: Maybe you ought to be thinking about Allium. Perhaps both Allium and sulfinic acids are worth a closer look. After all, leeks, garlic, onions and lesser known species of the odorous genus Allium have been used by man since the beginning of time as food, flavoring, condiments, ointments, salves, tinctures, plasters, enemas, medicines and decorations; for the use and benefit of man, to please the eye and gladden the heart; for taste and for smell, to strengthen the body and to enliven the soul.

NOTES



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APRIL 2, 1976

Studies in the Synthesis of Vernolepin. A Diels–Alder Approach to the Angularly Functionalized AB System

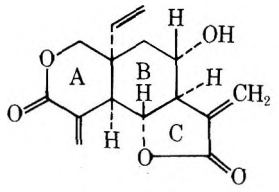
Samuel Danishefsky,* Paul Schuda, and Kuniki Kato

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received December 15, 1975

In model systems it has been demonstrated that the sequence (i) osmium tetroxide–barium chlorate, (2) lead tetraacetate–methanol–benzene, (3) lithium tri-*tert*-butoxyaluminum hydride may be used to convert conjugated cyclohexenones to valerolactones with excision of the α-carbon of the enone. A regiospecific and stereospecific Diels–Alder reaction of 2-methoxy-5-hydroxymethyl-1,4-benzoquinone (**25**) with 1-methoxy-1,3-butadiene (**26**) gave 2,8 β-dimethoxy-4aα-hydroxymethyl-5,8α-dihydronaphthalene-1,4-(8aαH,4aH)-dione (**27**). This was converted in five steps to 2β-formyl-2α-acetoxymethyl-4α,5α-oxido-6β-methoxycyclohexane-1β-acetic acid methyl ester (**43**). Treatment of the latter with lithium tri-*tert*-butoxyaluminum hydride gave a 19% yield of 8aα-acetoxymethyl-5β-methoxy-6α,7α-oxido-4aα-2-oxa-3-decalone (**45**) and a 46% yield of 4-acetoxymethyl-6-*exo*-methoxy-7-*endo*-hydroxy-2-oxabicyclo[3.2.1]octane-2-*exo*-acetic acid methyl ester (**46**). The stereochemistry of all intermediates and products is proven by taking advantage of intramolecular reactions.

A successful synthesis of the tumor inhibitor vernolepin (**1**)[1a,b] must provide simultaneous solutions to several novel structural problems. We perceive the most formidable of the obstacles to be the construction of the B ring in a stereochemical arrangement which allows for the elaboration of the C ring in its required form. An ancillary problem, whose seriousness cannot now be evaluated, involves the differentiation of the hydroxylactonic arrangements between vernolepin (**1**) and the related system, vernomenin (**2**).[1a,b] For instance, the data emanating from the structure elucidation do not allow for a confident prediction as to the mode of lactonization of a hypothetical precursor of the type **3**.



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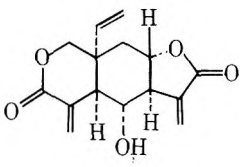
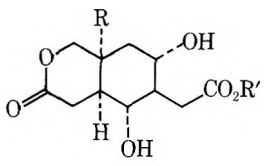


2, vernomenin



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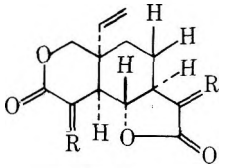
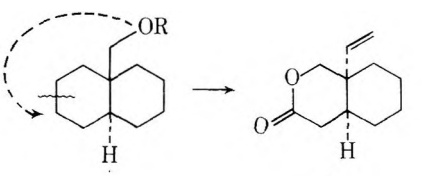


4, R = H
5, R = CH_2
(deoxyvernolepin)

The results of a variety of studies directed to the conversions of lactones to their α-methylene derivatives, most notably those of Grieco and co-workers,[2a,b,3] hold out the hope that the introduction of these functions may be postponed until the final stages of the synthetic effort. Particularly noteworthy in this respect is the transformation of **4** → **5** achieved by Grieco.[4] This work is clearly the most advanced synthttic contribution to the vernolepin problem thus far recorded.

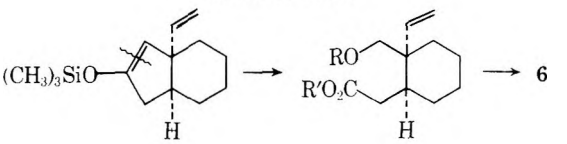
A successful synthesis must also deal with the construction of the cis-fused 2-oxa-3-decalone system bearing an angular function, susceptible of conversion to a vinyl group. Previous approaches directed toward the synthesis of **6** may be classified into two strategies. The approaches of Grieco[4,5a–c] and Marshall[6a,b] involve utilization of a trans-fused decalin, bearing latent hydroxymethyl functionality in the angular position. The C_2–C_3 bond is then cleaved. Carbons 1 and 2 become the vinyl group. The angular hydroxymethyl unit joins with an unravelled C_3 acyl group to afford a cis-fused 2-oxa-3-decalone.

Grieco[4,5] and Marshall[6] routes



6

Heathcock route[7]



7

A spectacular approach, due to Heathcock and Clark,[7] involves the simultaneous elaboration of a cis-fused hydrindene system (7) bearing an angular vinyl group and an endocyclic double bond which is part of a site specifically generated silyl enol ether. An ozonolysis–reduction sequence provides the elements for construction of a cis-fused 2-oxa-3-decalone.

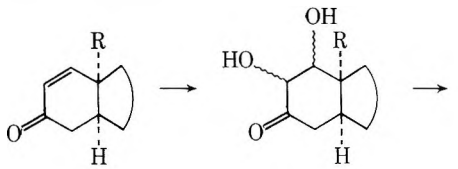
Our approach to this problem centered on the use of cis-fused hydronaphthalenes of the type 8.[8] A favorable element of this strategy appeared to be the availability of the required precursors by a Diels–Alder route. Woodward has demonstrated[9] the convertability of a methoxybenzoquinone adduct of 1,3-butadiene to a Δ^1-3-ketobicyclic system. It was our expectation that a Diels–Alder route lent itself well to variations of angular and ring B functionality in a fashion which might be conducive to attainment of the proper framework for attaching ring C.

The feasibility of oxidative cleavage of a conjugated cyclohexenone system, with excision of the α carbon and formation of a 4-acylbutyric acid derivative, is well known and has, in fact, been utilized in several total synthesis operations.[10a,b] The most commonly employed version of this reaction involves systems in which the β carbon of the enone is substituted and becomes a ketone after oxidation.

For our purposes, the oxidative cleavage must be performed on a substrate in which the β carbon is unsubstituted and is to be converted to an aldehyde. The success of the scheme depends rather critically on the preservation of the distinction in the oxidation levels of carbons 1 and 3 in precursor 8. Transformation of 8 to the secoacylaldehyde system, 10, and reduction of the latter would give the desired 11.

Fortunately, for our planning, there existed several precedents for the feasibility of converting 8 → 9 and, indeed for converting 8 → 10 and 10 → 11. The total synthesis of reserpine[11a] as well as modifications thereof[11b,c] provided a setting in which transformations of the type 8 → 9 and 9 → 10 (R = H) were studied. Furthermore, the conversion of Δ^1-3-keto steroids to 2-oxa-3-keto steroids[12a–c] involves the overall transformation of 8 → 11[13] via an intermediate of the type 10.

The route which we describe here involves a three-step sequence for transforming the bicyclenone to the bicyclic lactone. Glycolation is achieved by reaction of the enone with osmium tetroxide followed by oxidative or reductive work-up. The keto glycol 9 is cleaved by the action of lead tetraacetate in methanol–benzene.[12a] This reaction produces directly, and in high yield, the aldehyde methyl ester 10 (R = Me). Reaction of the general system 10 with lithium tri-*tert*-butoxyaluminum hydride provides the desired lactone, 11.[14] In the cases described below, the lactonization is spontaneous.



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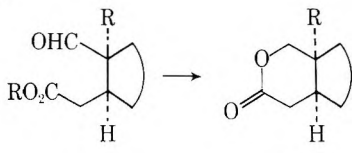
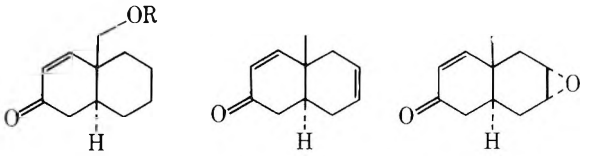


10 11

The method has been applied on a model basis to bicyclenenones 13a and 14. Compound 13a was prepared by



13, R = H 12 14

13a, R = Ac

acetylation of the known alcohol 13, prepared by the route of Mukharji.[15] Compound 14 was obtained by epoxidation of Woodward's dienone 12.[9] Although satisfactory combustion data were not obtained for this monoepoxide, its spectral properties (see Experimental Section) attest to its structure and homogeneity.

Our interest in demonstrating the viability of the transformations of the type 8 → 11 in the presence of an epoxide stems from the possibility that such a linkage may be of utility in elaborating the C ring of vernolepin. Thus, the opening of an epoxide by 1 equiv of $^-CH_2CO_2R$ constitutes a very promising route to trans-fused δ-lactones.

Reaction of 13 with osmium tetroxide in pyridine followed by cleavage with sodium bisulfite[12a] gave an 82% yield of the keto glycol 15, mp 99–100 °C. Treatment of 15 with lead tetraacetate in methanol–benzene[12a] afforded a quantitative yield of the crude aldehyde methyl ester 16. Substantial decomposition was encountered in attempted chromatographic purification of 16 on silica gel. Accordingly, the crude material, whose NMR spectrum was highly supportive of its structure, was used in the next step.

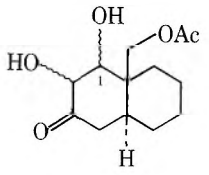
Upon reduction of compound 16 with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran a 62% (from 15) yield of the trans-fused acetoxylactone, 17, was obtained. It is interesting to note that, in principle, compound 16 lends itself to nonreductive transformation into a cis-fused lactone by utilizing the carbon bearing the acetate function as C_4 of the 2-oxadecalone. This strategy merges into the Grieco[5] and Marshall[6] pathways discussed earlier.

The formalism was reduced to practice by treatment of 16 with methanolic sodium hydroxide. The cis-fused 10-formyl-2-oxa-3-decalone (18) was obtained in 72% yield (from 15). It is seen that a cis- or trans-fused 4a acetoxymethyl functionalized 2-oxa-3-decalone.

Having demonstrated the basic viability of the approach, we tested its compatibility with internal epoxide functionality. Osmylation of 14 utilizing a catalytic amount (0.16 equiv) of osmium tetroxide in an aqueous solution containing barium chlorate[16] gave the crystalline keto glycol 19, mp 118–119 °C. As before, oxidative cleavage to aldehyde methyl ester 20 was achieved in high yield by the action of 19 with lead tetraacetate in methanol–benzene. Again, as before, reductive cyclization (lithium tri-*tert*-butoxyaluminum hydride) of 20 gave the trans-fused epoxyoxadecalone 21, mp 128–129 °C.

With the results of these model studies in hand we undertook a study of a route which held out some promise for reaching vernolepin itself. Although, as will be seen, the scheme did not prove serviceable in terms of the total synthesis objective, the work is suggestive of other pathways which might prove more successful. Furthermore, it is illustrative of the value of the Diels–Alder route for the synthesis of Δ^1-3-octalones bearing greater functionality than had been previously described.

We defined the trans-fused bicyclenone 22 as our intermediate objective. It was assumed that 22 could be converted to aldehyde methyl ester 23. Cleavage of the acetate function of 23 and nonreductive lactonization (cf. 16 → 18) would give the cis-fused oxadecalone 24 bearing an angular formyl group. It will be noted that, in principle, "back-



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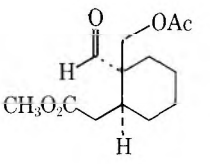

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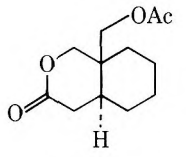

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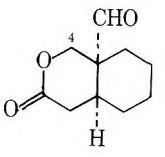

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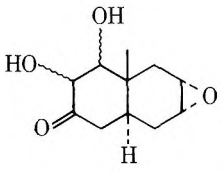

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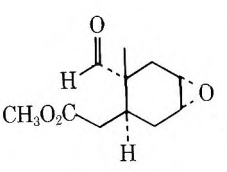

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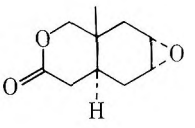

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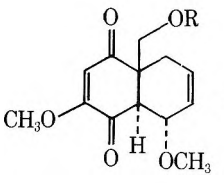
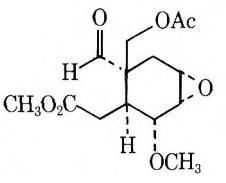
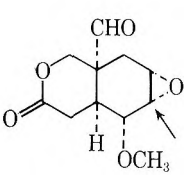


22, R = H or OAc



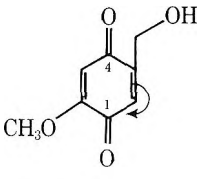
23



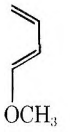
24

side" attack by a $^{-}CH_2CO_2R$ equivalent upon the epoxide bond at carbon 6 (see arrow) in structure **24** or a related congener[17] would give rise to a product in which the stereochemistry of the B ring has been properly arranged.

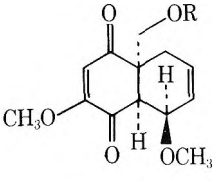
Our plan for reaching the trans-fused **22** involved a projected Diels–Alder reaction of **25** with 1-methoxybutadiene (**26**). It was anticipated that the major adduct would be **27.** This prediction follows from the supposition that of the ketonic groups in structure **25,** the one which is vinylogously conjugated to the ester (i.e., C_4 carbonyl) will be less electron deficient and thus less influential than the C_1 carbonyl in its orientational influence upon reaction with the electron-rich **26.**



25



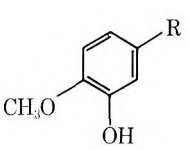
26



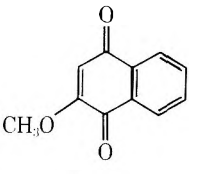
27, R = H
27a, R = Ac

It was further hoped that a cis product of the type **27** would be susceptible to epimerization, thus providing access to the trans series (cf. **22**).

Reduction of isovanillin (**28**) with sodium borohydride gave the known[18] phenol **29,** mp 132–133 °C. Upon treatment with Fremy's salt, **29,** suffered smooth oxidation,



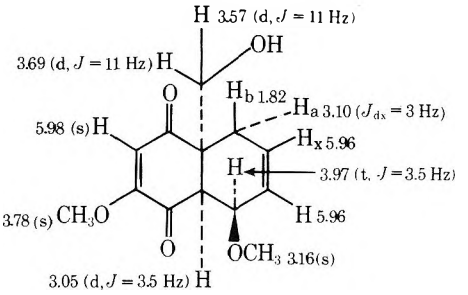
28, R = CHO
29, R = CH_2OH



30

thereby giving the required *p*-quinone **25,** 147–147.5 °C. In the event, Diels–Alder reaction of **25a** with **26** gave a 93% yield of crystalline **27,** mp 150–151 °C. We could find no evidence for the formation of any detectable amounts of positional or stereochemical isomers of **27.**

The most salient feature of the NMR spectrum (250 MHz) which resolves the orientational issue in **27** is the appearance of the allylic hydrogen on the carbon bearing the methoxyl (δ 3.97 ppm) as a triplet, $J_{H_8-H_{8a}} = 3.5$, $J_{H_8-J_{H_7}} = 3.5$ Hz. Correspondingly, the junction hydrogen at C_{8a} is seen as a doublet, δ 3.1 ppm, $J_{H_{8a}-H_8} = 3.5$ Hz. The observed ABX (δ_{H_B} 1.82; δ_{H_A} 3.10, $J_{AB} = 21$, $J_{BX} = <1$, $J_{AX} = 3$ Hz) rather than ABXY pattern for the allylic protons also defines the orientational issue. The remaining resonances are fully consistent with the proposed structure and are indicated.



27

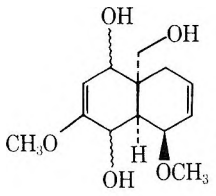
The stereochemical arrangement of **27** could not be argued altogether persuasively from the NMR spectrum. However, it was assumed that the cis junction expected from the Diels–Alder reaction had not undergone epimerization under the reaction conditions. Furthermore, the stereochemistry of the methoxyl group was assigned in the manner indicated on the basis of the principle of endo addition. As will be shown, both of these assumptions were, in fact, correct.

Unfortunately, all attempts to achieve the transformation of **27** or its derived acetate **27a,** mp 126–127 °C, to systems of the type **22** were without success. Even under mildly basic conditions (potassium acetate–methanol) either **27** or **27a** were converted to naphthoquinone **30,**[19] mp 183–184 °C, by the sum of β-elimination of methanol, retro-aldolization of the angular hydroxymethyl function (preceded by saponification in the case of **27a**), and air oxidation. Attempted epimerization of **27a** with diazabicycloundecene (DBU), in the hope of avoiding this unravelling, led to a complex mixture of components which was not separated. Conceivably β-elimination of methanol is the first step in this decomposition route.[20] The use of the nonnucleophilic base sodium hydride on **27b** also resulted in extensive decomposition.

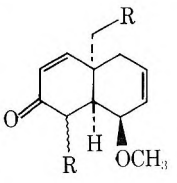
It is noted that the relative configuration of the hydrogens at C_{8a} and C_8 in the cis system **27** does not correspond to that required for vernolepin. An inversion of the oxygen stereochemistry at C_8 is thus required. Such inversion need not have been necessary if the sequence of **27** → **22** → **24** could have been achieved. Nevertheless, it was of interest to continue the synthesis in the cis series in the hope that such an inversion would be possible in the new target system **44** (vide infra).

Reaction of **27** with lithium aluminum hydride in tetrahydrofuran gave tetrahydro product **31,** mp 169–170 °C, in 60% yield. The α-ketol **32,** mp 100–101 °C, was obtained in 88% yield upon reaction of **31** with aqueous acid.[9] The acetoxydienone **32a,** mp 92–92.5 °C, was produced in near-quantitative yield by acetylation of **32** with pyridine and

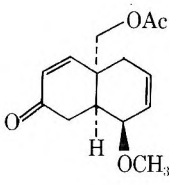
acetic anhydride. Reductive removal of the 4-acetoxy function was smoothly achieved (80%) by treatment of **32a** with chromous chloride in aqueous acetone.[20b] The required enone **33**, mp 84–84.5 °C, was thus available.



31



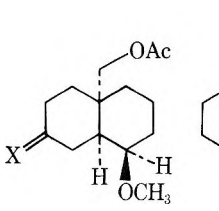
32, R = OH
32a, R = OAc



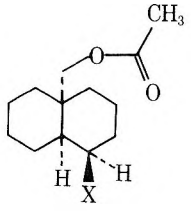
33

Before relating the results of experiments directed toward elaboration of the *cis*-2-oxa-3-decalone system, a series of transformations which defines the stereochemistry of centers 4a, 8, and 8a in compounds **27**, **31**, **32**, and **33** is described.

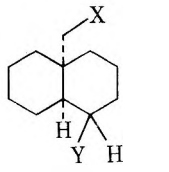
Catalytic reduction of **33** gives the tetrahydro product, **34**. The latter was transformed by a modified (Hirata conditions)[21] Clemmensen reduction to give the acetoxy ether **35**. Our next objective was the demethylation of **35**. It was expected that compound **36** would, upon deoxygenation of the secondary alcohol and saponification, afford **4a** hydroxymethyldecalin which is well known in both cis and trans forms.



34, X = O
35, X = H_2



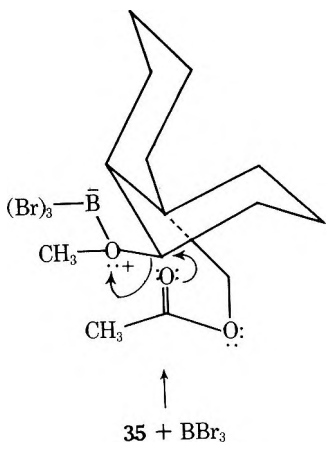
36, X = OH
37, X = Br
39, X = H



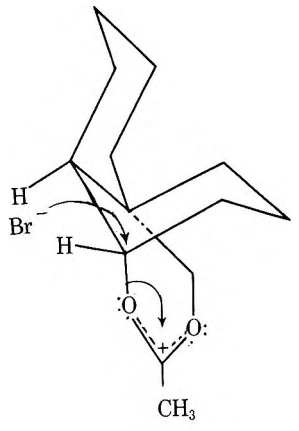
38, X = Br; Y = OAc
40, X = OH; Y = H

Accordingly, **35** was treated with boron tribromide in dichloromethane at 0 °C. Rather than the expected **36** there was obtained in 64% yield a compound of the formula $C_{13}H_{21}BrO_2$ whose infrared, NMR, and mass spectral properties defined it to be an acetoxy bromide. The uncertainty as to whether this compound was **37** or **38** was easily resolved in favor of the former. Thus, reaction of the acetoxy bromide with tri-*n*-butyltin hydride gave **39**. The latter was saponified to give the known[22] *cis*-**4a**-hydroxymethyldecalin (**40**). The material thus prepared was identical with an authentic sample of **40**. For further comparison, acetylation of authentic **40** gave an acetate identical with **39**.

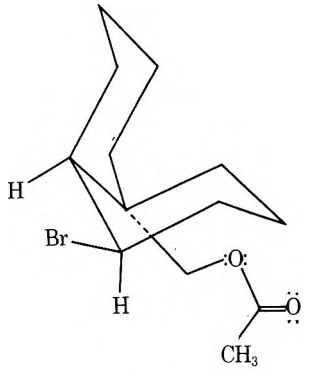
In addition to establishing the cis junction stereochemistry, we believe that this sequence also provides supporting evidence for a trans relationship between the methoxyl at position 1 and the angular acetoxymethyl group in compound **35** and thus in Diels–Alder adduct **27** as well as in compounds **31**–**35**. The conversion of **35** → **37** may be interpreted in terms of participation of the well-situated neighboring acetoxy function on the coordinated methoxyl group. Attack of bromide at the secondary carbon affords **37** rather than the alternate possibility, **36**, which would have been derived by attack at the neopentyl center of the acetoxonium species **35a**. The conversion of **35** → **35a** in preference to the usual demethylation (i.e., formation of **36**) is readily (though not uniquely) explained by the proposed configurational arrangement. By this view, the stereochemistry of **37** may also be formulated as shown, though this is not essential to our argument.



35 + BBr_3



35a



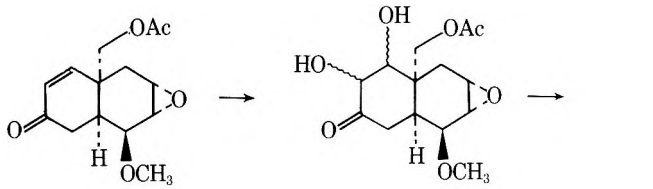
37

We now return to the conversion of **33** to a *cis*-3-oxa-2-decalone system. Reaction of **33** with *m*-chloroperbenzoic acid gave, in 64% yield, epoxy enone **41**, mp 107–108 °C. Though the reaction was slow and inefficient, necessitating long reaction times and large excesses of MCPBA,[23] there was no evidence for the formation of a diastereometric monoepoxide. The convex mode of epoxidation of **33**, which would have been predicted on the basis of precedent,[11a] would give rise to the stereochemistry shown in **41**. The correctness of this assignment of **41** will be proven by the subsequent (damaging) transformation of **43** → **46**.

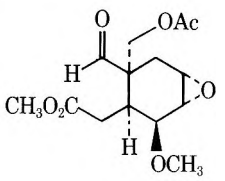
Osmylation of **41** followed by reductive work-up gave glycol **42**,[24] mp 183–184 °C, in 65% yield. Treatment of **42** with lead tetraacetate in benzene–methanol gave a quantitative yield of aldehyde ester **43**, albeit in crude form.

Reaction of **43** with lithium tri-*tert*-butoxyaluminum hydride in THF at 0 °C gave rise to a complex mixture which contained two principal products. The expected compound **45** was obtained but only in 20% yield. The major product of this reaction (46%) is a hydroxy ester [λ_{max} ($CHCl_3$) 2.95, 5.76 μ] whose molecular weight (*m/e* 302) indicates it to be a dihydro version of **43**. This compound, as well as **45**, presumably arises from **44a**, the dihydrometallic derivative of **43**.

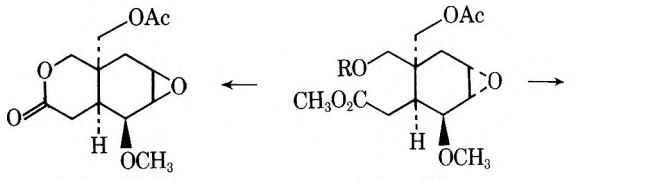
The *m/e* 302 compound did not undergo ring closure to give **45** under a variety of vigorous reaction conditions (heating in pyridine; reflux in benzene containing *p*-TsOH, etc). This nonreaction led us to tentatively reject the assignment of **44** to this substance. Oxidation of this dihydro product produced a ketone, $C_{14}H_{22}O_7$ (*m/e* 300), isomeric with aldehyde **43**. The NMR spectrum (250 MHz) of the ketone in conjunction with its origin and the origin of its precursor lead to the unambiguous assignments of **47** and **46**, respectively, to these compounds. Particularly decisive was the presence of isolated ABX and two AB systems in the NMR spectrum of **47**. The ABX defines with precision the point of attachment of the bridged ether.[25]



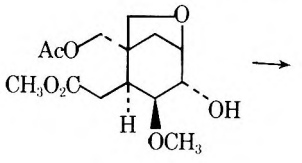
41 42



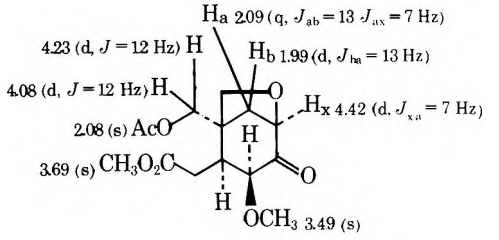
43



45 44, R = H
44a, R = Met



46



47

Apparently, intramolecular epoxide opening by the alkoxide elaborated after metal hydride reduction of aldehyde **43** competes all too effectively with intramolecular acylation. This internal alkylation does, however, serve to define the stereochemistry of the epoxides in compounds **41–43** as well as the target system, **45.**

While in principle, it might be imagined that the ratio of lactonization to epoxide opening would be a function of the metal ion found in **44a,** in practice reduction of **43** with sodium borohydride gave a similar ratio of **45:46.** In view of the consideration that **45** (vide supra) does not constitute an ideal intermediate for vernolepin in that inversion of the oxygen function at C_5 would, in any case, be required, this question was not pursued further.

Nevertheless we extract from these results the information that a cis-fused octalone bearing epoxide functionality in the B ring constitutes a viable precursor of a cis-fused 2-oxa-3-decalone system provided that reaction of the type **44** → **46** is prevented. In view of our recently developed easy access to the required octalones,[25] this approach to vernolepin is particularly attractive and is receiving intensive study in our laboratory.

Experimental Section[26]

Preparation of 4aβ-Acetoxymethyl-4a,5,6,7,8,8aα-hexahydronaphthalen-2(1*H*(-ONE (13a). To 320 mg (1.80 mmol) of hydroxy enone **13**[15] were added 5 ml of acetic anhydride and 5 ml of pyridine. The solution was stirred at room temperature under N_2 for 12 h. Evaporation of the volatiles afforded an oil which crystallized to afford 395 mg of crystalline **13a:** mp 51.5–52 °C (from ether); λ_{max} ($CHCl_3$) 55, 5.96 μ; δ ($CDCl_3$), 1.3–2.4 (m, 11), 2.0 (s, 3), 4.2 (d, *J* = 12 Hz, 1), 4.4 (d, *J* = 12 Hz, 1), 5.9 (d, *J* = 10 Hz, 1), 6.7 ppm (d, *J* = 10 Hz, 1).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.30; H, 8.21.

Preparation of 3ε,4ε-Dihydroxy-4aβ-acetoxymethyl-3,4,-4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (15). To a solution of 440 mg (1.98 mmol) of enone **13a** in 2 ml of pyridine was added a solution of 5.2 ml of 10% (w/v) OsO_4 in tetrahydrofuran. The solution was stirred at room temperature under N_2 for 18 h. A solution of 1.40 g of $NaHSO_3$ in 20 ml of water was added and stirring continued for 30 min. The solution was extracted with 6 × 75 ml of methylene chloride. Drying over anhydrous sodium sulfate followed by removal of the volatiles and trituration with 1:1 petroleum ether–ether afforded 413 mg (82%) of the keto glycol **15** as a light green, crystalline solid (mp 99–100 °C from ether): λ_{max} ($CHCl_3$) 2.92, 5.78, 5.82 μ; δ ($CDCl_3$) 1.3–2.4 (m, 11), 2.0 (s, 3), 4.0–4.7 ppm (m, 4).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.64; H, 7.69.

Preparation of 2β-Acetoxymethyl-2α-formylcyclohexane-1β-acetic Acid Methyl Ester (16). To a solution of 400 mg (1.56 mmol) of **15** in 63 ml of absolute methanol and 31 ml of benzene was added 2.10 g (4.74 mmol) of lead tetraacetate (freshly recrystallized from glacial acetic acid). The reaction mixture turned yellow upon mixing. After several hours the mixture turned colorless. Stirring under N_2 was continued for 18 h. The volatiles were removed in vacuo and the residual oil dissolved in 50 ml of water and was extracted with 4 × 60 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 400 mg of a light yellow residue, which was taken to be compound **16:** λ_{max} ($CHCl_3$) 3.52, 3.70, 5.75 μ; δ ($CDCl_3$) 1.2–2.8 (m, 11), 2.0 (s, 3), 3,6 (s, 3), 4.2 (broadened s, 2), 9.4 ppm (s, 1).

Preparation of *trans*-4a-Acetoxymethyl-3-oxadecal-2-one (17). To a solution of 240 mg (0.94 mmol) of aldehyde ester **16** in 13 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) at 0 °C was added 300 mg (1.19 mmol) of lithium tri-*tert*-butoxyaluminum hydride. The solution was allowed to warm to room temperature and stirred under N_2 at room temperature for 1 h. The solution was poured into ca. 15 ml of ice water and acidified with 1% HCl. The aqueous solution was extracted with 4 × 50 ml of ethyl acetate. These were combined and dried over anhydrous Na_2SO_4. The volatiles were removed in vacuo leaving 202 mg of a residual oil which was chromatographed on 15 g of silicic acid using 3:2 benzene–ethyl acetate for elution. Lactone **17,** 134 mg (63%), was obtained as an oil (R_f 0.45, 3:2 PhH–EtOAc): λ_{max} ($CHCl_3$) 5.77 μ (br); δ ($CDCl_3$) 1.2–2.6 (m, 11), 2.2 (s, 3), 3.4–4.6 ppm (m, 4).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.84; H, 8.26.

Preparation of *cis*-4a-Formyl-3-oxadecal-2-one (18). To a solution of 390 mg (1.52 mmol) of aldehyde ester **16** in 5.6 ml of absolute methanol at room temperature was added 3.50 ml of a 5% KOH in methanol solution. The solution was stirred at room temperature for 13 min and diluted with 33 ml of water. Acidification with 5% HCl and extraction with 6 × 30 ml of EtOAc followed by drying over anhydrous Na_2SO_4 and removal of the volatiles afforded 270 mg of a viscous oil. The oil was chromatographed on 20 g of silicic acid using 3:2 benzene–ethyl acetate for elution. There was obtained 200 mg (72%) of lactone **18** as an oil (R_f 0.40, 3:2 PhH–EtOAc): λ_{max} ($CHCl_3$) 3.48, 3.68, 5.72 μ (br); δ ($CDCl_3$) 1.2–2.8 (m, 11), 4.4 (d, *J* = 15 Hz, 1), 4.6 (d, *J* = 15 Hz, 1), 9.5 ppm (s, 1).

Preparation of 4aβ-Methyl-6α,7α-oxido-4a,5,6,7,8,8aα-hexahydronaphthalen-2-(1*H*)-one (14). To a solution of 3.47 g (0.02 mmol) of *m*-chloroperbenzoic acid in 20 ml of CH_2Cl_2 under N_2 at 0 °C was added 2.52 g (0.02 mmol) of dienone **12.** The mixture was stirred at 0 °C for 2 h. The CH_2Cl_2 solution was stirred with 20 ml of 10% Na_2SO_3 for 30 min. The organic layer was washed with 10% $NaHCO_3$, water, and saturated NaCl successively and dried over anhydrous Na_2SO_4. Upon evaporation of the volatiles in vacuo there was obtained 2.65 g of a residue which was chromatographed on 40 g of silicic acid using $CHCl_3$ for elution. Epoxy enone **14,** 2.09 g (77%), was obtained as an oil (R_f 0.13, $CHCl_3$): λ_{max} ($CHCl_3$) 5.93 μ; δ ($CDCl_3$) 1.02 (s, 3), 1.7–2.3 (m, 7), 3.2 (br s, 2), 5.8 (d, *J* = 10 Hz, 1), 6.5 ppm (d, *J* = 10 Hz, 1).

Preparation of 3ε,4ε-Dihydroxy-6α,7α-oxido-4aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (19).[24] To a solution of 255 mg (1.10 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ in 13.5 ml of

water under N_2 added 1.00 g (4.00 mmol) of epoxide. To the stirred suspension was added 1.70 ml of a 10% (w/v) solution of OsO_4 in tetrahydrofuran. The black suspension was stirred at room temperature for 5 h. Another 525 mg (2.10 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ was added and stirring was continued for 43 h. During this time the solution became clear. A solution of saturated NaCl (28 ml) was added and the aqueous mixture was extracted with 6 × 50 ml of chloroform. The organic layers were combined and dried. The solvents were evaporated to leave 1.08 g of a oil which crystallized upon trituration with ether. There was thus obtained 602 mg (53%) of compound **19** as light gray crystals.

Chromatography of the 406 mg of mother liquors on 25 g of silica gel using 7:3 chloroform–acetone as an eluent afforded an additional 40 mg of **19**, mp 118–119 °C (R_f 0.35, 7:3 $CHCl_3$–Me_2CO): λ_{max} ($CHCl_3$) 2.77, 5.83 μ; δ ($CDCl_3$) 1.18 (br s, 3), 1.6–2.8 (m, 9), 3.22 ppm (br s, 2).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.96; H, 7.58.

Formation of 2β-Methyl-2α-formyl-4α,5α-oxidocyclohexane-1β-acetic Acid Methyl Ester (20). To a solution containing 91 ml of absolute methanol, 46 ml of benzene, and 500 mg (2.40 mmol) of glycol **19** was added 3.20 g (7.20 mmol) of $Pb(OAc)_4$ (freshly recrystallized from glacial acetic acid). The mixture turned orange-yellow immediately. Within 1 h the mixture had turned colorless. It was allowed to stir under N_2 for 14 h. The solvents were evaporated in vacuo and the resulting oil dissolved in 40 ml of water. The water solution was extracted with 4 × 120 ml of ethyl acetate. The ethyl acetate extracts were washed with 25 ml of saturated brine. The brine solution was extracted once more with 120 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. After evaporation of the solvents and the acetic acid in vacuo, the residual oil, 500 mg (100%), taken to be aldehyde ester **20**, was used in the next step: λ_{max} ($CHCl_3$) 3.42, 3.60, 5.74 μ (br); δ ($CDCl_3$) 1.0 (s, 3), 1.5–2.6 (m, 7), 3.2 (br s, 2), 3.6 (s, 3), 9.3 ppm (s, 1).

Preparation of *trans*-4aβ-Methyl-6α,7α-oxido-3-oxadecal-2-one (21). To a solution containing 465 mg (2.20 mmol) of crude aldehyde ester 20 in 22 ml of dry (distilled from $LiAlH_4$) tetrahydrofuran at 0 °C was added 581 mg (3.90 mmol) of $LiAl(O\text{-}t\text{-}Bu)_3H$ with stirring. The mixture was allowed to stand for 10 min at 0 °C and then allowed to warm to room temperature. It was stirred under N_2 at room temperature for 1 h. The reaction mixture was poured into ice water (~20 ml) and acidified with 1% HCl. The solution was extracted with 4 × 100 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. The solvents were evaporated to afford an oil which upon trituration with ether afforded 210 mg (53%) of **21** as off-white crystals, mp 128–129 °C. The mother liquors from the trituration were chromatographed using 15 g of silicic acid and 9:1 chloroform–acetone as an eluent. This afforded another 30 mg (7.5%) of lactone **21** (R_f, 9:1 $CHCl_3$–Me_2CO, 0.45): λ_{max} ($CHCl_3$) 5.76 μ; δ ($CDCl_3$) 1.0 (s, 3), 1.5–2.7 (m, 7), 3.2 (m, 2), 3.9 (d, J = 11 Hz, 1), 4.0 ppm (d, J = 11 Hz, 1).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.74; H, 7.96.

Preparation of 3-Hydroxy-4-methoxybenzyl Alcohol (29). To an ice-cold solution containing 50.00 g (0.33 mmol) of isovanillin (**28**) and 500 ml of absolute ethanol was added dropwise with stirring over a period of 10 min a solution of 12.50 g (0.33 mmol) of sodium borohydride in 312 ml of absolute ethanol. The color changed from light yellow to turbid white during the addition. The reaction mixture was allowed to warm to room temperature over 45 min. The solution was acidified with 5% HCl. The reaction mixture was extensively extracted with chloroform. The organic extracts were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvents afforded a white solid which was washed with a small amount of ether and sucked dry after filtration to give 41.60 g (83.9%) of a white, crystalline solid: mp 132–133 °C (lit.[18] 132 °C); λ_{max} ($CHCl_3$) 2.84 μ; δ ($CDCl_3$) 3.90 (br s, 1), 3.92 (s, 3), 4.6 (s, 2), 5.6 (s, 1), 6.6–7.0 ppm (m, 3).

Preparation of 2-Methoxy-5-hydroxymethyl-1,4-benzoquinone (25). A solution of 11.80 g (0.08 mmol) of phenol **29** dissolved in a minimum amount of $CHCl_3$ and ether was added to a vigorously stirred solution of 45 g (0.19 mmol) of Fremy's salt[27] in 2000 ml of H_2O and 200 ml of 1/6 M KH_2PO_4 at 0 °C. The mixture was stirred at 0 °C for 30 min and extracted with 3 × 300 ml of methylene chloride. The aqueous solution was saturated with solid KCl and again extracted with 3 × 200 ml of methylene chloride. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to afford brownish yellow crystals which upon washing with ether gave 9.56 g (74%) of quinone **25** as a bright yellow, crystalline compound: mp 147–147.5 °C; λ_{max} ($CHCl_3$) 2.80 (br), 5.92, 6.02, 6.19 μ; δ ($CDCl_3$) 2.2 (br s, 1), 3.8 (s, 3), 4.5 (br s, 2), 5.8 (s, 1), 6.6 ppm (t, J = 1.6 Hz, 1).

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.98; H, 4.72.

Diels–Alder Reaction of 25 with 1-Methoxy-1,3-butadiene (26). Formation of Adduct 27. A solution of 7.50 g (0.045 mmol) of quinone **25** and 7.50 g (0.089 mmol) of diene (Aldrich) **26** in 150 ml of absolute methanol was heated under reflux under N_2 for 3 h. The reaction mixture was orange at the outset and after a time turned light yellow. The solution was cooled to ambient and the volatiles were evaporated in vacuo. A yellow, crystalline residue was obtained which when washed with a small amount of ether afforded 9.54 g (86%) of **27** as a light yellow, crystalline solid. Cooling of the ether solution afforded 980 mg of impure **27** which was recrystallized from benzene to give an additional 820 mg of adduct (7%) **27**: mp 150–151 °C; λ_{max} ($CHCl_3$) 2.78, 5.84, 6.00, 6.17 μ; δ ($CDCl_3$) (see structure **27**).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.06, H, 6.40.

Preparation of 2,8β-Dimethoxy-4aα-hydroxymethyl-1,4,-4a,5,8,8aα-hexahydronaphthalene-1ε,4ε-diol (31). To a suspension of 6.25 g (0.16 mmol) of $LiAlH_4$ in 50 ml of dry (distilled from $LiAlH_4$) tetrahydrofuran was added with stirring and external cooling a solution of 6.00 g (0.024 mmol) of adduct **27** in 140 ml of dry tetrahydrofuran over a period of 30 min. After addition was complete, the mixture was refluxed under N_2 for 5 h and then allowed to stand overnight. A solution of saturated NH_4Cl was slowly added until the excess $LiAlH_4$ was neutralized. Solid anhydrous Na_2SO_4 (20 g) was then added followed by 700 ml of CH_2Cl_2. The mixture stirred for 30 min. The salts were filtered and washed with 3 × 700 ml of methylene chloride and 2 × 700 ml of ethyl acetate. The combined filtrates were evaporated to afford a white solid which, upon washing with a small amount of ether, gave 3.88 g (60%) of pure **31** as white crystals, mp 169–170 °C, λ_{max} (KBr) 2.75 μ.

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.80; H, 8.08.

Preparation of 1ε-Hydroxy-4aα-hydroxymethyl-8β-methoxy-4a,5,8,8aα-tetrahydronaphthalen-2(1*H*)-one (32). To a solution of 3.51 g (0.014 mmol) of triol **31** in 35 ml of methylene was added 35 ml of 10% H_2SO_4 (w/v). The two-phase system was stirred vigorously under N_2 for 2.5 h at room temperature. The solution was poured into 150 ml of saturated KCl and then extracted with 6 × 30 ml of methylene chloride and with 3 × 300 ml of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvents left a clear oil. To the oil was added 6 ml of 1:1 ether–CH_2Cl_2. The insoluble portion was removed. The solvents were evaporated from the filtrate and this residue crystallized from ether–hexane to afford 2.70 g (88%) of pure **32**, mp 100–101 °C, λ_{max} ($CHCl_3$) 2.75, 5.86 μ.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.30; H, 7.20.

Preparation of 1ε-Acetoxy-4aα-acetoxymethyl-8β-methoxy-4a,5,8,8aα-tetrahydronaphthalen-2(1*H*)-one (32a). To a solution of 2.71 g (0.012 mmol) of diol in 40 ml of pyridine was added 40 ml of acetic anhydride. The mixture was stirred under N_2 for 12 h at room temperature. The liquids were evaporated in vacuo and a viscous oil remained which crystallized to afford 3.64 g (98%) of a yellowish solid: mp 92–92.5 °C; λ_{max} ($CHCl_3$) 5.68, 5.82 μ; δ ($CHCl_3$) 2.1 (s, 3), 2.2 (s, 3), 2.4 (br s, 2), 2.7 (t, J = 10 Hz, d, J = 3 Hz, 1), 3.3 (s, 3), 3.8 (t, J = 10 Hz, 1), 4.0 (d, J = 11 Hz, 1), 4.2 (d, J = 11 Hz, 1), 5.8–6.4 ppm (m, 5).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 61.90; H, 6.23.

Preparation of 4aα-Acetoxymethyl-8β-methoxy-4a,5,8,8aα-tetrahydronaphthalen-2(1*H*)-one (33). To a vigorously stirred solution of 0.8 g of $HgCl_2$ in 10 ml of water was added 10 g of Zn dust. Th mixture was stirred for 5 min and the aqueous solution decanted. To the moist residue was added 20 ml of water and 2 ml of concentrated HCl. The flask was flushed with CO_2 (from dry ice) for 5 min. Finely pulverized chromium(III) chloride (5.0 g) was added with vigorous stirring and CO_2 was continuously allowed to flush through the system. After several minutes the green color turned to a royal blue. The mixture was stirred under CO_2 for 1 h at room temperature at which time it was ready for use. The reagent was used immediately. A flask containing a solution of 3.08 g (0.010 mmol) of the enone diacetate in 600 ml of acetone was flushed for 10 min with CO_2 (from dry ice). A solution of $CrCl_2$ as

prepared above (1200 ml) was introduced via syringe while CO_2 still passed over the system. The solution was stirred at room temperature for 55 min whereupon it was extracted with 6 × 500 ml of ether. The organic layer was evaporated to approximately 150 ml and then washed with 10% $NaHCO_3$. The ether was dried over anhydrous Na_2SO_4. Concentration of the ether afforded 1.78 g (71%) of **33** as pure white needles and 0.72 g of an oil which had essentially the same TLC as the crystals. Chromatography of the oil on 20 g of silicic acid and elution with 9:1 chloroform–acetone afforded an additional 226 mg (9%) of crystalline enone monoacetate: mp 84–84.5 °C; λ_{max} ($CHCl_3$) 5.70, 5.91 μ; δ ($CDCl_3$) 2.1 (s, 3), 2.1 (m, 2), 2.28 (d of d, J_{AB} = 18, J_{AC} = 14 Hz, 1), 2.61 (d of d, J_{BA} = 18, J_{BC} = 5 Hz, 1), 2.76 (d of t, J_{CA} = 14, J_{CB} = 5 Hz), 4.00 (br s, 1), 4.10 (d, J = Hz, 1), 4.13 (d, J = 11 Hz, 1), 5.72–5.78 (m, 2), 5.98 (d J = 10 Hz, 1), 6.70 ppm (d, J = 10 Hz, 1).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.12; H, 7.18.

Preparation of 4aα-Acetoxymethyl-8β-methoxy-3,4,4a,5,-6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (34). A solution of 800 mg (3.20 mmol) of acetoxyenone **33** in 40 ml of ethyl acetate was hydrogenated on a glass hydrogenator at atmospheric pressure over 80 mg of 10% Pd/C for 18 h. The mixture was filtered through Celite and the catalyst washed with three 100-ml portions of ethyl acetate. The ethyl acetate was evaporated in vacuo. The residual oil crystallized upon standing to afford 812 mg (99%) of **34:** mp 69–70 °C (from ether); λ_{max} ($CHCl_3$) 5.78, 5.87 μ; δ ($CDCl_3$) 1.2–2.4 (m, 13), 2.1 (s, 3), 3.2–3.4 (m, 1), 3.2 (s, 3), 4.4 ppm (br s, 3).

Preparation of 4aα-Acetoxymethyl-8β-methoxy-8aα-decahydronaphthalene (35). To a solution of 710 mg (2.80 mmol) of decalone **34** in 50 ml of anhydrous ether at 0 °C was added slowly, in small portions, 3.00 g (46.15 mmol) of activated (0.5% HCl) Zn over a period of 10 min. The mixture was stirred vigorously at 0 °C for 1 h. The Zn was filtered and washed with three 50-ml portions of anhydrous ether. The combined ether layers were washed with 3 × 25 ml of saturated $NaHCO_3$, and then with water. After drying over sodium sulfate the solution was concentrated in vacuo to afford 665 mg of **35** which was used without further purification: λ_{max} (film) 5.77 μ; δ ($CDCl_3$) 1.3–2 (m, 15), 2.1 (s, 3), 4.1 ppm (m, 3).

Formation of 4aα-Acetoxymethyl-8β-bromo-8aα-decahydronaphthalene (37). To a solution of 900 mg (3.75 mmol) of **35** in 20 ml of CH_2Cl_2 (which had been passed through a column of neutral alumina) at 0 °C was then added a solution of 1.80 g (7.17 mmol) of BBr_3 in 3 ml of CH_2Cl_2. The solution was stirred at 0 °C under N_2 for 1.5 h. To this system was added 30 ml of water and stirring was continued for 15 min. The reaction mixture was diluted with 100 ml of CH_2Cl_2 and the aqueous layer well extracted. The organic layers were combined, washed with saturated brine, and dried over anhydrous Na_2SO_4. Removal of the volatiles afforded an oil (820 mg). TLC analysis showed four spots (7% ethyl acetate in *n*-hexane). Chromatography of the oil on 30 g of silicic acid using 7% ethyl acetate in *n*-hexane afforded 466 mg (46%) of the acetoxy bromide **37** (R_f 0.35, 4% ethyl acetate in *n*-hexane): λ_{max} (film) 5.70 μ; δ ($CDCl_3$) 1.3–2.0 (15), 2.1 (s, 3), 4–4.2 ppm (m, 3).

Preparation of *cis*-4a-Acetoxymethyldecalin (39). To a solution of 39 mg (0.13 mmol) of acetoxy bromide **37** in 0.5 ml of benzene at 5 °C was added 60 mg (0.21 mmol) of tri-*n*-butyltin hydride. The solution was stirred under N_2 at room temperature for 24 h. Four drops of concentrated HCl were added and stirring continued overnight at room temperature under N_2. Anhydrous Na_2SO_4 was added, the mixture filtered, and the Na_2SO_4 washed with 20 ml of $CHCl_3$. The combined organic solutions were evaporated in vacuo to an oil. Preliminary chromatography was conducted on 2 g of silicic acid using *n*-hexane as eluent. However, slight amounts of tin compounds containing tin still remained. Preparative TLC using 5% ether in *n*-hexane afforded 14 mg (52%) of compound **39** as an oil: λ_{max} (film) 5.76 μ; δ ($CDCl_3$) 1.5 (m, 17), 2.1 (s, 3), 4.1 ppm (s, 2).

Saponification of 39. Formation of *cis*-4a Hydroxymethyldecalin (40). To a solution of 13 mg (0.06 mmol) of **39** in 1 ml of anhydrous methanol was added a solution of 8 mg (0.15 mmol) of KOH in 1 ml of methanol. After 10 min at room temperature the solution was poured into 1 ml of water and extracted with four 5-ml portions of $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield 10 mg (98%) of an oil which crystallized at −78 °C from petroleum ether to afford pure **40:** mp 59–60 °C (lit.[22] 59.4–60.2 °C); NMR spectrum ($CDCl_3$) δ 1–1.8 (m, 18), 3.6 ppm (s, 2). The NMR spectrum of this material was identical with that of the authentic sample. Also, acetylation as the authentic alcohol gave an acetate, the NMR and infrared spectra of which were identical with those of **39** in all respects.

Preparation of 4aα-Acetoxymethyl-6α,7α-oxido-8β-methoxy-4a,5,6,7,8,8aα-hexahydronaphthalen-2(1*H*)-one (41). To a solution of 3.04 mg (0.018 mmol) of *m*-chloroperbenzoic acid in 150 ml of methylene chloride was added 4.00 g (0.016 mmol) of enone acetate. The mixture was stirred at room temperature under N_2 for 24 h. On the basis of TLC analysis of the reaction progress, an additional 3.04 g of peracid was added at 24-h intervals for the next 3 days. After a total reaction time of 96 h, the solution was treated with 350 ml of 10% sodium sulfite for 30 min. The CH_2Cl_2 layer was extracted with 5% $NaHCO_3$, then with H_2O, and finally with saturated NaCl. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated to give a yellow oil. This, on trituration with 1:1 ether–petroleum ether, gave 2.77 g (64%) of **41:** mp 107–108 °C; λ_{max} ($CHCl_3$) 5.71, 5.92 μ; δ ($CDCl_3$) 1.8–4.0 (m, 8), 2.0 (s, 3), 3.4 (s, 3). 4.1 (d, 2), 6.0 (d, J = 9 Hz, 1), 6.8 ppm (d, J = 9 Hz, 1).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.18. Found: C, 62.59; H, 6.60.

Osmylation of Enone 41. Formation of 3ϵ,4ϵ-Dihydroxy-4aα-acetoxymethyl-6α,7α-oxido-8β-methoxy-3,4,4a,5,6,7,8,8a-α-octahydronaphthalen-2(1*H*)-one (42). To a solution of 400 mg (1.12 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ in 11.75 ml of water was added 450 mg of (1.69 mmol) of enone **41.** To this was added 0.10 ml of a solution of 10% OsO_4 in tetrahydrofuran and the reaction mixture stirred under N_2 for 5 h. The solution turned black during this time. An additional 400 mg (1.12 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ was added and the solution slowly became turbid. After an additional 15 h of stirring under N_2, 10 ml of water and 25 ml of freshly prepared 10% $NaHSO_3$ were added and the solution stirred for 5 min. Extraction with 6 × 50 ml of methylene chloride, drying the organic layers over anhydrous Na_2SO_4, and evaporation of the volatiles in vacuo afforded an oil. Upon trituration with 5 ml of 1:1 petroleum ether–ether, 285 mg (63%) of glycol **42** was obtained as a white, crystalline solid. The dark residues were chromatographed on 7 g of silicic acid using 7:3 $CHCl_3$–acetone to afford an additional 11 mg (3%) of **42:** mp 183–184 °C (R_f 0.24, 7:3 $CHCl_3$–Me_2CO); λ_{max} ($CHCl_3$) 2.93 (br), 5.83 μ; *m/e* 300 (P).

Preparation of 2β-Formyl-2α-acetoxymethyl-4α,5α-oxido-β-methoxycyclohexane-1β-acetic Acid Methyl Ester (43). To a solution of 200 mg (0.67 mmol) of **42** in 35 ml of absolute methanol and 16 ml of benzene was added 900 mg (2.03 mmol) of $Pb(OAc)_4$ (freshly recrystallized from glacial acetic acid). The solution turned dark yellow immediately. After several hours it turned colorless, and was combined under N_2 for 15 h. The volatiles were removed in vacuo and the resulting oil dissolved in 20 ml of water. The aqueous solution was extracted with 4 × 120 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo, leaving 200 mg of oily **43:** λ_{max} (liquid film) 3.55, 3.70, 5.76 μ; δ ($CDCl_3$) 2.0 (s, 3), 2.1–2.8 (m, 5), 3.1–3.6 (m, 3), 3.5 (s, 3), 3.7 (s, 3), 4.1 (br s, 2), 9.7 ppm (s, 1).

Reduction of 43. Formation of 8aα-Acetoxymethyl-5β-methoxy-6α,7α-oxido-4aα,2-oxa-3-decalone (45) and 4-Acetoxymethyl-6-*exo*-methoxy-7-*endo*-hydroxy-2-oxabicyclo[3.2.1]-octane-5-*exo*-acetic Acid Methyl Ester (46). To a solution of 400 mg (1.33 mmol) of **43** in 27 ml of dry tetrahydrofuran at −78 °C under N_2 was added 400 mg (1.57 mmol) of $LiAl(O\text{-}t\text{-}Bu)_3H$. The solution was stirred at −78 °C under N_2 for 7 min and allowed to warm to room temperature. The volatiles were removed in vacuo. To the semisolid mass was added 25 ml of 1% HCl. The aqueous system was extracted with 4 × 150 ml of ethyl acetate. The combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and evaporated to afford 750 mg of a yellow, oily residue. The oil was slowly chromatographed on 32 g of silicic acid using 9:1 chloroform–acetone. From the chromatography was recovered 380 mg from which 71 mg (20%) of lactone **45** as an oil (R_f 0.38, 9:1 $CHCl_3$–Me_2CO) and 184 mg (46%) of bridged ether **46** were obtained (R_f 0.20, 9:1 $CHCl_3$–Me_2CO), mp 125 °C (sublimes). **46:** λ_{max} ($CHCl_3$) 2.97, 5.75 μ (br); δ ($CDCl_3$) 1.76 (d of d, J_{AB} = 12, J_{AX} = 6 Hz, 1), 2.18 (d, J_{BA} = 12 Hz), 1.88 (br s, 1), 2.07 (s, 3), 2.40 (d of d, J_{AB} = 15, J_{AX} = 5 Hz, 1), 2.59 (d, J_{BA} = 15 Hz), 2.63–2.73 (m, 2), 3.31 (s and m, 4), 3.37 (s, 1), 3.40 (br t, 1), 3.70 (s, 1), 3.93–4.10 (m, 4), 4.34 ppm (t, J_{XA} = 6 Hz, 1). **45:** λ_{max} ($CHCl_3$) 5.78 μ (br); δ ($CDCl_3$) 1.76 (d of d, J_{AB} = 15, J_{AX} = 3 Hz, 1), 1.97 (d of d, J_{BA} = 15, J_{BX} = 2 Hz, 1), 2.01 (s, 3), 2.32 (m, 1), 2.38 (d of d, J_{AB} = 14, J_{AX} = 6 Hz, 1), 2.54 (d of d, J_{BA} = 14, J_{BX} = 6 Hz), 3.19 (m, 1), 3.23 (m, 1), 3.41 (s, 3), 3.63 (m, 1), 3.86 (d, J = 9 Hz, 1), 3.89 (d, J = 9 Hz), 3.96 (d, J = 9 Hz), 4.01 ppm (d, J = 9 Hz).

Oxidation of Alcohol of 46. Formation of Ketone 47.[28] To a

solution of 21.5 mg (0.09 mmol, l 1.5 equiv) of pyridinium chlorochromate[28] in 1.5 ml of methylene chloride was added a solution of 20 mg (0.06 mmol) of alcohol in 2 ml of methylene chloride. The solution was stirred at room temperature under N_2 and monitored by TLC (9:1 $CHCl_3$–acetone). After 4 h almost no alcohol was left. The solution was transferred to a column of 4 g of Florisil and filtered using 50 ml of methylene chloride, then 50 ml of 9:1 methylene chloride–acetone. The volatiles were removed in vacuo to yield an oil which was chromatographed via preparative TLC to afford 13 mg of ketone (67%) as an oil (R_f 0.64, 9:1 $CHCl_3$–acetone).

Attempted Epimerization of 27. Formation of 2-Methoxynaphtho-1,4-quinone (30).[29] To a solution of 294 mg (1.00 mmol) of **27** in 7 ml of methanol was added 98 ml (1.00 mmol) of potassium acetate. The solution was refluxed under air ebullition for 2 h.[29] Additional methanol was added as necessary to maintain a volume of approximately 7 ml. The dark mixture was cooled to room temperature and air ebullition continued for 2 h. The mixture was poured into 60 ml of $CHCl_3$ and extracted with 20 ml of water. The aqueous layer was extracted with 5 × 10 ml of chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford a solid residue. Washing with 1:1 ether–petroleum ether afforded 163 mg (87%) of **30:** mp 183–184 °C (lit.[19] 181–182 °C); λ_{max} ($CHCl_3$) 5.92, 6.03, 6.19, 6.23, 6.32 μ; δ ($CDCl_3$) 3.9 (s, 3), 6.2 (s, 1), 7.6–8.3 ppm (m, 4).

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(11) (a) R. B. Woodward, F. F. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2,** 1 (1958); (b) for osmium tetroxide–barium chlorate followed by periodic acid cleavage see L. Blahay, J. Weichet, J. Zvacek, and B. Kakac, *Collect. Czech. Chem. Commun.*, **25,** 237 (1960); (c) for ozonolytic method see K. Pelz, L. Blaha, and J. Weichet, *ibid.*, **21,** 1160 (1961).
(12) (a) R. Hirschmann, N. G. Steinberg, and R. Walker, *J. Am. Chem. Soc.*, **84,** 1270 (1962); (b) R. Pappo and C. J. Jung, *Tetrahedron Lett.*, 365 (1962); (c) L. N. Nystead and R. Pappo, U.S. Patent 3,109,016 (1963); *Chem. Abstr.*, **60,** 3045*f* (1964).
(13) The first full account of the conversion of Δ^2-cyclohexenones → valerolactones as part of a vernolepin oriented approach involves an ozonolytic fragmentation of the type used in the reserpine[11c] and 2-oxasteroid[12c] syntheses; see C. G. Chavdarian and C. H. Heathcock, *J. Org. Chem.*, **40,** 2970 (1975). In our hands, the ozonolysis method works well in the case of the ring B unsubstituted series (**13a** → **16**) but fails in the presence of a ring B epoxide (**14** → **20**) as well as other functional groups.
(14) It is interesting to note that in the oxasteroid series,[12a] reductive cyclization of systems such as **10** was not achieved in one step from the aldehyde ester in the manner achieved in our work. Rather, it was necessary to proceed via the corresponding aldehydo acids of **12b** and **12c.** The utilization of the easily available and easily handled aldehyde ester system of the type **10** in conjunction with lithium tri-*tert*-butoxyaluminum hydride to reach lactone **11** is an important advantage in more highly functionalized and labile systems.
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(16) Cf. A. S. Kende, T. J. Bentley, R. A. Mader, and D. Ridge, *J. Am. Chem. Soc.*, **96,** 4332 (1974).
(17) It will be noted that in system **24** itself the preferred conformation of this cis decalin in conjunction with the principle of trans-diaxial opening of epoxides would probably result in nucleophilic attack at C_6 rather than C_7 as required. Thus a comprehensive strategy must make provisions for unmobilizing the cis decalin in such a fashion as to freeze that conformation (angular function and C_8 function axial to ring B) which is required to direct opening at C_8.
(18) N. Mauthner, *J. Prakt. Chem.*, **158,** 321 (1941).
(19) L. F. Fieser, *J. Am. Chem. Soc.*, **70,** 3165 (1948).
(20) E. J. Corey and R. Wollenberg, *J. Org. Chem.*, **40,** 2265 (1975). For an example of enolization conducted in such a way as to preserve a vinylogous β-aldol see E. J. Corey and C. Cyr, *Tetrahedron Lett.*, **1761** (1974).
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(23) In our hands, attempted applications of the Kishi high-temperature epoxidation on **33** gave a more complex reaction mixture; see Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugrura, and H. Kakoi, *J. Chem. Soc., Chem. Commun.*, 64 (1972).
(24) The stereochemistry of the glycol centers in **15, 19,** and **42** is not assigned. In each case, the compounds are homogeneous.
(25) The formal alternative structural possibility resulting from attack of the alkoxide of **44a** upon carbon 7 of the epoxide to produce an oxabicyclo[2.2.2]octane system could not be rigorously eliminated by the NMR spectrum of what we assign to be **46.** However, the isolated ABX array in the derived ketone (**47**) would not be possible in the ketone derived from such a process. It is possible that one of the several minor unidentified products could be derived from such a pathway.
(26) Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 Infracord spectrophotometer. NMR spectra were at 60 MHz on Varian A-60D or Varian T-60 spectrometers. The spectra of **21, 25, 32, 45,** and **46** were measured at 250 MHz. Spectra were measured in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) from Me_4Si. Low-resolution mass spectra were measured on an LKB-9000 system by direct insertion. High-resolution mass spectra were measured on a Varian CH_5 system. TLC measurements were conducted on Merck silica gel plates 60F-254.
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(28) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(29) In attempted epimerizations of compound **27** without air ebullition complex mixtures of compound 30 and 1,4-dihydroxy-2-methoxynaphthalene were generated.

Synthetic Studies toward Complex Diterpenoids. IX.[1,2] A New Stereocontrolled Synthetic Route to Some Intermediates for Diterpenoid Alkaloids and C_{20} Gibberellins

Usha R. Ghatak* and Sephali Chakrabarty

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700032, India

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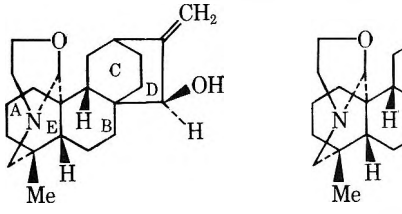
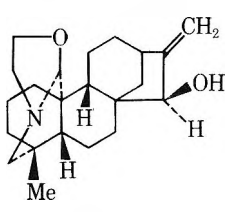
Stereocontrolled syntheses of (±)-*N*-acetyl-19,20-imino-13-methoxypodocarpa-8,11,13-triene (**1b**) and the corresponding demethoxy compound (**1a**), established synthetic intermediates for diterpenoid alkaloids and C_{20} gibberellins, are reported. The synthetic approach contains a novel method of angular alkylation based upon a regioselective intramolecular α-oxocarbenoid insertion across the benzylic C–H (at C-10) bond in the copper-catalyzed carbenoid decomposition of the easily accessible α-diazomethyl ketones **6a** and **6b** to the corresponding bridged tetracyclic ketones **8a** and **8b.** These have been converted, in high yields, to the respective dicarboxylic acids **11a** and **11b** through oxidation of the corresponding hydroxymethylene derivatives **10a** and **10b,** which were finally transformed to **1a** and **1b** through an efficient route. The ketone **8a** has been converted to the C-10 homologous dicarboxylic acid **13a.**

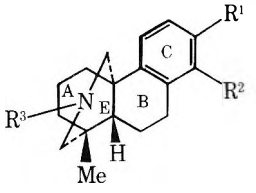
A great deal of attention in the past two decades toward complex diterpenoid alkaloids[3] has led to the total synthesis[4,5] of atisine, veatchine, synthetic intermediates, and related model compounds.[6,7] With a solitary exception,[4c] all the successful total synthetic approaches consist in the construction first of the heterocyclic E ring in an octahydrophenanthrene system such as **1c** or **1d** containing ring A, B, and C, followed by elaboration of the bridged-ring systems D through the aromatic moiety. The former synthon has also been utilized in the solitary total synthesis of a C_{20} gibberellin, gibberellin A_{15}, by Nagata and his coworkers.[8] The crucial problem in the synthesis of the tetracyclic amine synthons lies in the introduction of the C-4, C-10 (diterpene numberings) functionalized carbon residues in a *trans*-hydrophenanthrene moiety. In spite of the notable achievements in the total synthesis of diterpene alkaloids, there are only a limited number of methods so far available for satisfactory realization of this objective. These can be classified only in three narrow groups, namely (1) intramolecular functionalization of C-4 or a C-10 angular methyl group in an appropriately constructed tri-[6a,d-f] or tetracyclic[4c,6l] system; (2) intramolecular alkylation[4d,6g,h] at C-4 in a tricyclic system through a functionalized C-10 angular methyl group; and (3) by conjugated addition of hydrocyanic acid.[4a] The methods included under 1 and 2 suffer not only from low yields and multiplicity in their reaction paths, but also from the synthetic problems associated with the starting materials containing at least two to three asymmetric centers. The hydrocyanation method[9] has so far been proved to be the best for allowing the synthesis of the tetracyclic synthon, e.g., **1c,** on a large scale; however, it is clearly necessary to pay great attention to the reaction conditions and reagents as well as the nature of the substrates.[10] Our long-range and comprehensive synthetic endeavors in this area[2] have culminated in a new simple synthetic method for stereospecific introductions of C-4 and C-10 functionalized carbon residues in a *trans*-hydrophenanthrene moiety leading to a few key intermediates for the synthesis of complex diterpenoids, including the tetracyclic acetylamine synthons **1a** and **1b.** The notable feature of this route lies in the angular alkylation at a classically nonreactive center through the C-4 diazoacetyl group via long-range regioselective intramolecular α-oxocarbenoid insertion[11] across the C-10 benzylic C-H σ bond in copper-catalyzed carbenoid decompositions in the diazo ketones **6a** and **6b** in which the stereochemistry of all the three asymmetric centers is already fixed at the early stage of the synthesis.



atisine



veatchine

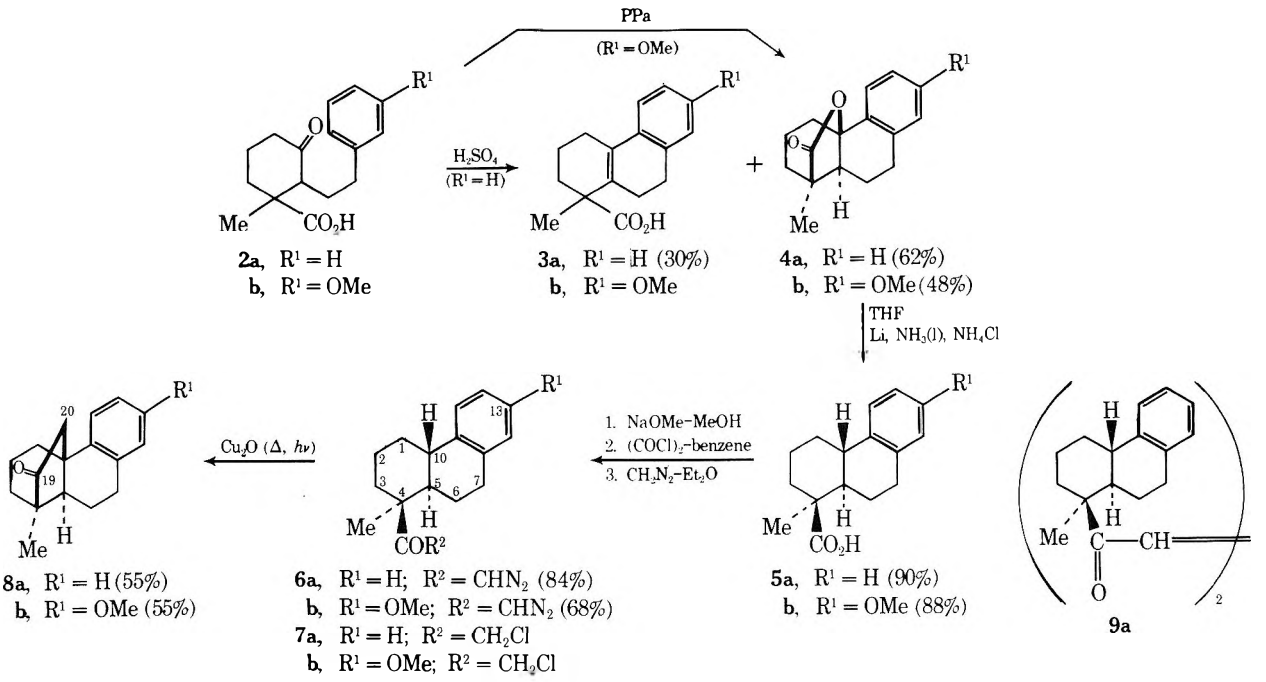


1a, $R^1 = R^2 = H$; $R^3 = Ac$
b, $R^1 = OMe$; $R^2 = H$; $R^3 = Ac$
c, $R^1 = OMe$; $R^2 = R^3 = H$
d, $R^1 = H$; $R^2 = OMe$; $R^3 = Ac$

Simple stereospecific syntheses of the parent carboxylic acids **5a**[12] and **5b**[13] of the requisite diazo ketones were developed in this laboratory from the readily accessible starting materials through the respective unsaturated acids **3a** and **3b** and the lactones **4a** and **4b.** This two-step sequence for the synthesis of the lactones has been further simplified in the present study. While cyclization of the keto acid **2a**[14] with polyphosphoric acid (PPA), according to Mori et al.,[15] gave the lactone **4a** only in 30–35% yield in our hands (reported[15] yield 53%), repeating the reaction using H_2SO_4 at low temperature afforded the desired lactone **4a** in 62% yield along with the unsaturated acid **3a** in 30% yield. Attempted H_2SO_4-catalyzed cyclization of the methoxy keto acid **2b** did not give satisfactory results. However, PPA-induced reaction of **2b**[13] yielded the lactone **4b** in 48% yield. In the present studies reductive cleavages of the lactones **4a** and **4b** have been modified[12,13] by using lesser amounts of lithium metal without any detrimental effect on the yields of the corresponding acids **5a** and **5b.**

The crude acid chlorides obtained from the reactions of the dry sodium salts of the acids **5a** and **5b** were treated with an excess of ethereal diazomethane solution in the presence of triethylamine. The crystalline diazo ketones **6a** and **6b** were obtained in good yields. The required transformations of the diazo ketones **6a** and **6b** to the corresponding tetracyclic ketones **8a** and **8b** were achieved in a satis-

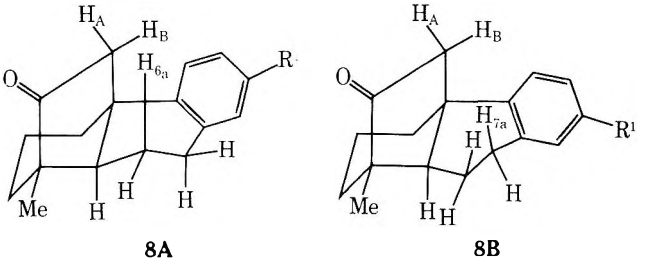
Scheme I



factory yield after extensive experimentations.[16] Best results were obtained when intramolecular alkylation was effected by thermal decomposition of dilute solutions of the crystalline diazo ketones in THF–cyclohexane in the presence of freshly prepared Cu_2O under irradiation[11d,17] with tungsten lamps. Under these conditions decomposition of the diazo ketone **6a** afforded the known tetracyclic ketone **8a** in 53–55% yield along with the dimeric compound **9a** in 5–10% yield as the only isolable crystalline products after chromatography on alumina. The ketone **8a** is identical with an authentic sample[6h] with respect to mixture melting point and ir comparisons.[18] The structure of the dimeric ketone **9a** has been assigned on the basis of ir and NMR spectral data (see Experimental Section). Thermal decomposition of the crystalline diazo ketone **6a** in THF–cyclohexane in the presence of anhydrous $CuSO_4$ gave the tetracyclic ketone 8a in 50–54% yield as the only isolable crystalline product. However, using crude diazo ketone in the carbenoid decomposition under the above condition the desired ketone **8a** was isolated in 45–50% yield along with the chloro ketone **7a,** in variable yields (2–5%) after chromatography. The formation of the chloro ketone can be partly or completely supressed by using triethylamine in the conversion of acid chloride to diazo ketone. The structure of the chloro ketone **7a** has been assigned on the basis of ir, NMR, and elemental analyses (see Experimental Section).

The crystalline methoxy diazo ketone analogue **6b** on thermal decomposition under irradiation with a tungsten lamp in the presence of Cu_2O gave the desired tetracyclic ketone **8b** in 50–54% yield as the only isolable crystalline product after chromatography. Thermal decomposition of the diazo ketone **6b** in the presence of $CuSO_4$ gave the product **8b** in 38% yield. When the noncrystalline crude diazo ketone was used in the above reaction besides the tetracyclic ketone (20–25% yield), a small amount of chloro ketone **7b** (see Experimental Section) was also isolated after chromatography. The methoxy tetracyclic ketone **8b** showed a single strong five-membered ketone carbonyl band in the ir and a methoxyoctahydrophenanthrene chromophore in the uv. The final confirmation of the assigned structure for **8b** came from comparing a 220-MHz ^1H NMR spectrum of this ketone with that of the demethoxy analogue **8a** of established structure. In ^1H NMR (220 MHz in $CDCl_3$) spectra both the ketones **8a** and **8b** showed the C-4 Me singlet at δ 1.045; the OMe singlet in **8b** appeared at δ 3.78. The most important structural features common to **8a** and **8b** are the protons on the methylene bridge adjacent to the ketone carbonyl ($-COCH_2-$), which appeared as doublets and a pair of doublets centered at δ 2.32 and 2.47 (J_{AB} = 20 Hz), and δ 2.31 and 2.45 (J_{AB} = 20 Hz) in the ketones **8a** and **8b,** respectively. The small coupling (ca. 1.5 Hz) of the proton at higher fields, assigned to the H_B (shielded by aromatic ring), possibly arises with the proton H_{6a} or H_{7a} in the conformations **8A** and **8B,** respectively, in these compounds. The exact conformation of the B ring, however, could not be evaluated from these data.[19]

8A and **8B**

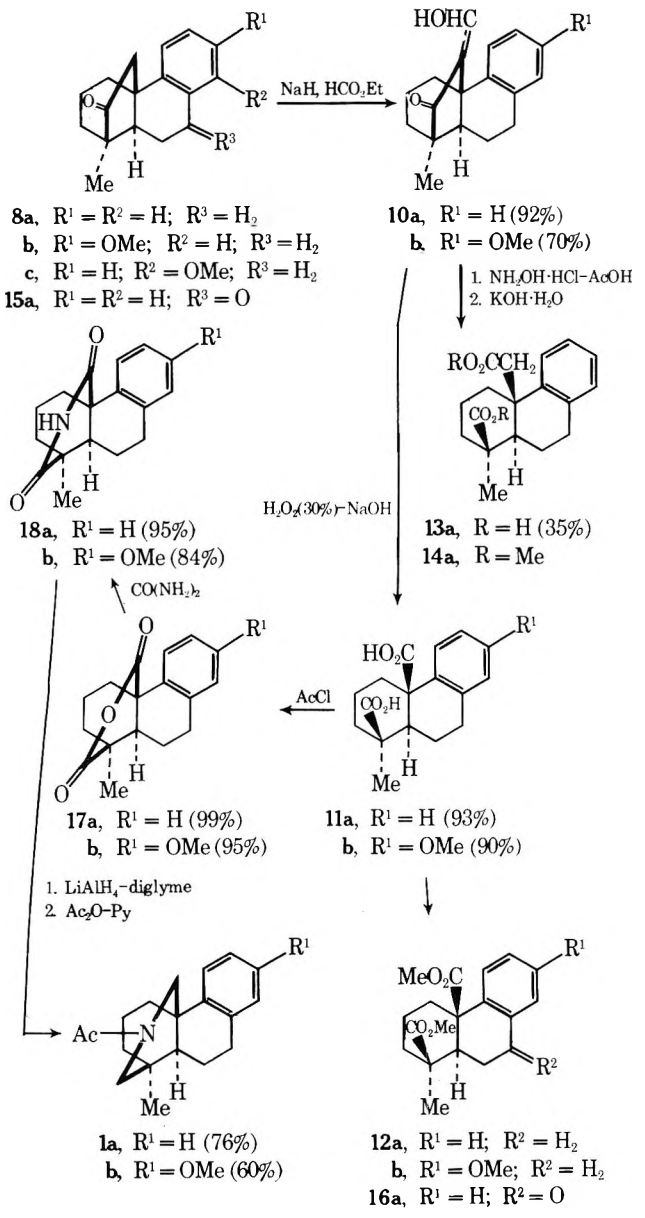


8A **8B**

With the establishment of the structures of the ketones **8a** and **8b,** it is clearly evident that the intramolecular oxocarbenoid insertion is highly regioselective[16] in the respective diazo ketones. Next, attention was devoted to the developments of the C-4, C-10 functionalities of the diterpenoids from the ketones **8a** and **8b.** Recently, Matsumoto et al.[6h] have reported conversions of **8a** and **8c** to the corresponding tetracyclic acetylamines **1a** and **1d.** Other approaches[4d,6g] toward similar transformations, developed earlier, are less satisfactory. We have now succeeded in elaborating an efficient sequence of reactions (Scheme II) which not only provides a route to the tetracyclic amine derivatives for the diterpenoid alkaloids, but also some intermediates **11a, 11b,** and **13a** with C-4, C-10 functions suitable for preparation of C_{20} gibberellins[20] and other complex diterpenoids.[21]

Condensation of the ketone 8a with ethyl formate in the presence of a large excess of sodium hydride under forcing

Scheme II



conditions[22] afforded the crystalline hydroxymethylene derivative **10a** in 92% yield. The same condensation using sodium methoxide gave only 19% of the desired product. On oxidation[23] with alkaline hydrogen peroxide, **10a** yielded the dicarboxylic acid **11a** in 93% yield; the dimethyl ester **12a** was obtained by esterification with diazomethane. Attempted ozonolysis of **10a** followed by in situ oxidation with hydrogen peroxide gave a complex mixture from which the diacid **11a** could be isolated in ca. 12% yield. Reaction of the hydroxymethylene ketone **10a** with hydroxylamine hydrochloride in acetic acid, followed by basic cleavage[24] of the resulting product, afforded the C-10 homologous dicarboxylic acid **13a** in 30% yield; dimethyl ester **14a**, mp 100 °C. The required transformation of the methoxy ketone **8b** to **11b** was satisfactorily achieved following the sequence developed for the demethoxy analogue and is summarized in Scheme II. The demethoxy ketone **8a** and the diester **12a** were also transformed to the corresponding 7-oxo compounds **15a** and **16a** by oxidation with chromic acid.

The final stage was now set for the development of the nitrogen containing hetereocyclic E ring of the diterpenoid alkaloids in the dicarboxylic acids **11a** and **11b** following the sequence developed by Tahara et al.[6e] for a similar transformation. The dicarboxylic acids **11a** and **11b** afforded the corresponding anhydrides **17a** and **17b** in 95–98% yield, which were converted to the respective imides **18a** and **18b** in 95 and 84% yield, respectively. The reduction of the imide **18a** under forcing conditions with lithium aluminum hydride in diglyme and subsequent acetylation of the crude amine furnished the tetracyclic acetylamine **1a** in 76% yield. It was proved to be identical with the sample derived through an independent synthetic route[6h] by mixture melting point and comparative ir spectrum.[18] In a similar sequence the methoxyimide **18b** was converted to the tetracyclic acetylamine **1b.** This was proved to be completely identical with a sample (prepared by Tahara[6e] from Nagata's[4a] racemic sample of the tetracyclic amine **1c**) of **1b** by mixture melting point, ir spectrum, and GLC retention times in two different columns.[25]

The tetracyclic base **1c** served as the key intermediate in the total synthesis of racemic atisine,[4a] veatchine,[4b] and gibberellin A_{15}.[8] Thus the stereospecific introduction of the C-4, C-10 cis dicarboxylic acid functionalities in a podocarpane (*trans*-hydrophenanthrene) moiety has been achieved through a new stereocontrolled intramolecular angular alkylation[26] reaction, thereby solving a crucial problem in the total syntheses of a large number of complex diterpenoids.

Experimental Section

The compounds described are all racemates. Melting points are uncorrected. Petroleum ether used in chromatography refers to the fraction of bp 60–80 °C and light petroleum refers to the fraction of bp 40–60 °C. Chromatography on neutral alumina was performed using aluminum oxide "standardized for chromatographic analysis acc. to Brockmann" purchased from M/S Sarabhai M. Chemicals. The homogeneity of all compounds was checked by TLC on silica gel G (200 mesh) plates of 0.2 mm thickness using benzene–ethyl acetate and benzene–methanol solvent systems. The spots were located by exposing the dried plates in iodine vapor. Uv spectra were determined in 95% ethanolic solution on a Beckman DU spectrophotometer and unless otherwise mentioned, ir spectra were determined in chloroform solution on a Perkin-Elmer Model 21 double beam recording spectrophotometer by Mr. A. Ghosal. NMR spectra were recorded on a Varian HA-60 spectrometer and Me_4Si as internal standard in $CDCl_3$; 220-MHz NMR spectra were obtained from the Varian Analytical Instrument Division, Palo Alto, Calif. Analyses were performed by Mrs. C. Dutta of this laboratory.

4aβ-Hydroxy-1α-methyl-1,2,3,4,4a,9,10,10a-*trans*-octahydrophenanthrene-1β-carboxylic Acid 1→4a Lactone (4a) and 1-Methyl-1-carboxy-1,2,3,4,9,10-hexahydrophenanthrene (3a).[27] a solution of the keto acid **2a** (26.0 g, 0.01 mol) in dry thiophene-free benzene (50 ml) was added to well-stirred concentrated sulfuric acid (350 ml), cooled in an ice–salt bath (ca. −10 to −5 °C), during 10–15 min and the stirring in the cold was continued for 2 h. The reaction mixture was poured onto crushed ice and extracted with ethyl acetate. The organic extract was thoroughly washed with 2% sodium hydroxide solution and water, dried (Na_2SO_4), and concentrated to afford 15.1 g (62%) of the lactone **4a**, mp 129–130 °C. A portion of this on recrystallization once from ethyl acetate–petroleum ether afforded **4a** in colorless prisms, mp and mmp 130–131 °C (lit.[12] 130–131 °C) (ir spectrum identical with that of an authentic sample). The combined aqueous alkaline extracts were acidified with 6 N hydrochloric acid and the separated white solid acid was extracted with ethyl acetate, washed with water, dried (Na_2SO_4), and evaporated. The residual product was recrystallized twice from CH_2Cl_2–methanol to give 7.3 g (30%) of **3a**, mp and mmp 180–181 °C (lit.[12] mp 180–181 °C) (ir spectrum identical with that of the previously prepared sample[12]).

(±)-20-Nordeoxypodocarpic Acid (5a). The lactone **4a** (3.5 g, 14.5 mmol) in anhydrous ether (40 ml) and dry tetrahydrofuran (40 ml) was subjected to reductive cleavage with liquid ammonia (ca. 350 ml) and lithium metal (400 mg, 57.6 mg-atoms) using solid ammonium chloride as proton donor, following exactly the method described earlier.[12] The crude product on recrystallization once from ethyl acetate–petroleum ether afforded 3.15 g (90%) of **5a**: mp and mmp 189–190 °C (lit.[12] 180–190 °C); ir spectrum identical with that of the previously prepared sample.[12]

4aβ-Hydroxy-1α-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-

***trans*-octahydrophenanthrene-1β-carboxylic Acid 1→4a Lactone (4b).** To a well-stirred mixture of PPA, prepared from phosphorus pentoxide (30 g) and orthophosphoric acid (24 ml, 85% w/w), at room temperature was added the keto acid **2b** (6.0 g, 22 mmol) in ether (10 ml) and the stirring was continued for 1 h. The temperature of the reaction mixture was then raised to 50 °C and the mixture was stirred for an additional 30 min. The cooled reaction mixture was poured onto crushed ice and the organic material was extracted with ethyl acetate, washed with 2% sodium hydroxide solution and water, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and crystallization from ethyl acetate–petroleum ether afforded the lactone **4b** (2.40 g), mp and mmp 171 °C (lit.[13] mp 171–172 °C) (ir spectrum identical with that of the previously prepared sample[13]). The alkaline washings on acidification and reextraction gave an acidic fraction (2.4 g) which on recyclization–lactonization under the above condition gave another crop of lactone **4b** (310 mg) (total yield 48%).

(±)-13-Methoxy-20-nordeoxypodocarpic Acid (5b). Reductive cleavage of the lactone **4b** (1.2 g, 4.4 mmol) using lithium metal (130 mg, 18.7 mg-atoms) in liquid ammonia (ca. 200 ml) according to the conditions described earlier[13] afforded the acid **5b** (950 mg, 88%), mp and mmp 165–166 °C (lit.[13] 165–166 °C) after recrystallization of the crude product from methanol. Ir spectrum was identical with that of the previously prepared sample.[13]

(±)-4β-Diazoacetyl-19,20-bisnorpodocarpa-8,11,13-triene (6a). The acid **5a** (4.0 g, 16.4 mmol) in benzene (100 ml) was titrated to neutrality with a solution of sodium methoxide in methanol (phenolphthalein indicator). After removal of the solvent, the residue was freed from traces of moisture and methanol by distillation with benzene. The dried sodium salt was suspended in anhydrous benzene (150 ml) containing pyridine (0.2 ml) and cooled in an ice bath and oxalyl chloride (5 ml, 58.6 mmol) was added. The mixture was stirred in the cold for 30 min and at 60 °C for 1 h, cooled, and filtered and the filtrate was evaporated under reduced pressure. An ethereal solution (200 ml) of the resulting crystalline acid chloride was added dropwise with stirring to an ice-cold ethereal diazomethane solution (generated from 10 g of *N*-methylnitrosourea) containing triethylamine (2.3 ml, 16.4 mmol) and left overnight. This was filtered and the filtrate evaporated to afford the crude diazo ketone **6a**, purified by filtering through a column of neutral alumina (30 g) and eluting with ether–petroleum ether (3:7). The diazo ketone **6a** was obtained as a pale yellow solid (3.75 g, 84%), mp 127–128 °C dec. Recrystallization from ether afforded the analytical sample, mp 127–128 °C dec, ir 2110 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51. Found: C, 75.59; H, 7.42.

Intramolecular Insertion Reactions. Transformations of 6a to (±)-19,20-Cyclopodocarpa-19-oxo-8,11,13-triene (8a). Method A. With Cuprous Oxide under Thermal–Photochemical Decomposition.[27] A solution of the above diazo ketone **6a** (2.5 g, 9.3 mmol) in a mixture of anhydrous tetrahydrofuran–cyclohexane (400 ml, 1:1) was added during 5 h with stirring to a refluxing suspension of anhydrous cuprous oxide (8 g) in cyclohexane (300 ml) under irradiation with two 250-W tungsten lamps and the refluxing was continued for another 2 h (diazo ketone band in ir disappeared). The catalyst was filtered off and the solvent was evaporated under reduced pressure to afford a gummy solid which was chromatographed on neutral alumina (50 g) and eluted with petroleum ether to afford **8a** as a white solid (1.25 g, 55%), mp 116–117 °C. Recrystallization from light petroleum gave the analytical sample: mp and mmp 117–118 °C (lit.[6h] mp 118 °C); ir (KBr) spectrum was identical with that of the sample previously prepared by a different route;[6h,18] λ_{max} 266 nm (log ε 2.65), 274 (2.64); NMR (220 MHz) δ 1.045 (s, 3 H, $-CH_3$), 1.20–1.75 (complex m, 9 H, $-CH_2$ and $-CH<$), δ_A 2.32 (d, 1 H, J_{AB} = 20 Hz), δ_B 2.47 (dd, 1 H, J_{AB} = 20, J_B, H_{6a}, or J_B, H_{7a}, ≃ 1.5 Hz), 2.84 (m, 2 H, $-CH_2Ar$), 7.18 (m, 4 H, $-C_6H_4-$); mass spectrum (70 eV) *m/e* (rel intensity) 240 (M^+, 72), 224 (79), 205 (31), 195 (49), 180 (58), 165 (38), 150 (39), 130 (49), 120 (69), 90 (100).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.80; H, 8.39.

Petroleum ether–benzene (3:1) eluents gave a solid fraction contaminated with some oil, which on recrystallization yielded the dimeric product **9a** (220 mg, 10%): mp 153 °C; ir 1670 cm^{-1}; NMR δ 1.26 (s, 6 H, 2 CH_3), 1.42–2.71 (br m, 12 H, saturated $-CH_2-$), 2.67–3.44 (br m with two br s at 2.75 and 2.83, 12 H, remaining $-CH_2-$ and methine), 5.61 (br m, 2 H, $-CH=CH-$), 7.0–7.20 (br m, 8, 2 ArC_6H_4).

Anal. Calcd for $C_{34}H_{40}O_2$: C, 84.95; H, 8.39. Found: C, 84.85; H, 8.42.

Method B. Thermal Decomposition with Copper Sulfate. Thermal decomposition of the diazo ketone **6a** (2.0 g, 7.42 mmol) in a mixture of anhydrous cyclohexane (400 ml)–tetrahydrofuran (160 ml) in the presence of anhydrous copper sulfate (6 g) following the procedure described above required 8 h for complete reaction. After usual work-up and chromatography of the product on neutral alumina (60 g) using petroleum ether as eluent, there was obtained 970 mg (54%) of the bridged ketone **8a**, mp and mmp 117–118 °C.

Method C. Decomposition of Crude 6a with Copper Sulfate. When the crude diazo ketone **6a** prepared from the acid **5a** was used in the above reaction, the bridged ketone **8a** was isolated in variable yields ranging from 45 to 50%. In some cases, the chloro ketone **7a** could be separated in 2–5% yields, especially when triethylamine was not used during the preparation of the diazo ketone. The chloro ketone **7a** was obtained in the petroleum ether eluted fraction along with the bridged ketone **8a** during the chromatography of the insertion product and was separated by fractional crystallization from petroleum ether: mp 133 °C; ir 1715 cm^{-1}; λ_{max} 266 nm (log ε 2.72), 274 (2.69); NMR δ 1.33 (s, 3 H, CH_3), 1.83 (m, 6 H, saturated $-CH_2$ and $CH<$), 2.83 (m, 2 H, $-CH_2Ar$), 3.47 (br s, $-COCH_2Cl$), 7.17 (m, 4 H, $-C_6H_4-$).

Anal. Calcd for $C_{17}H_{21}OCl$: C, 73.79; H, 7.59. Found: C, 74.08; H, 7.62.

(±)-4β-Diazoacetyl-13-methoxy-19,20-bisnorpodocarpa-8,11,13-triene (6b). The diazo ketone **6b** was prepared from the acid **5b** (1.0 g, 3.6 mmol) in an exactly similar manner as described for its demethoxy analogue. The crude yellow semisolid product was purified by filtering through a short column of neutral alumina (15 g) and eluting with ether–petroleum ether (3:7) to afford the crystalline pale yellow diazo ketone **6b** (750 mg, 68%), mp 108–110 °C dec. Recrystallization from ether gave the analytical sample, mp 108–110 °C dec, ir 2115 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}O_2N_2$: C, 72.45; H, 7.43. Found: C, 72.01; H, 7.37.

Further elution with ether–petroleum ether (1:1) afforded a yellow gum which did not solidify.

Intramolecular Insertion Reaction. Transformation of 6b to (±)-19,20-Cyclopodocarpa-13-methoxy-19-oxo-8,11,13-triene (8b). Method A. With Cuprous Oxide under Thermal–Photochemical Decomposition. The diazo ketone **6b** (500 mg, 1.68 mmol) in anhydrous tetrahydrofuran (50 ml) and cyclohexane (50 ml) was added to a stirred refluxing suspension of cuprous oxide (2 g) in cyclohexane (100 ml) under irradiation with two 250-W tungsten lamps during 2 h and refluxed for another 2 h (disappearance of the diazo ketone band in ir). Removal of the solvent from the filtrate yielded a solid product which was dissolved in a minimum amount of benzene and chromatographed on neutral alumina (8 g). Elution with benzene–petroleum ether (1:3) afforded the desired ketone **8b** (250 mg, 55.5%), mp 129–130 °C. Recrystallization from light petroleum afforded the analytical sample: mp 130 °C; ir 1735 cm^{-1}; λ_{max} 276 nm (log ε 3.55); NMR (220 MHz) δ 1.045 (s, 3 H, CH_3), 1.20–1.75 (m, 9 H, $-CH_2-$ and $-CH<$), δ_A 2.31 (d, 1 H, J_{AB} = 20 Hz), δ_B 2.45 (dd, 1 H, J_{AB} = 20, J_B, H_{6a}, or J_B, H_{7a}, ≃ 1.5 Hz), 2.84 (m, 2 H, $-CH_2Ar$), 3.78 (s, 3 H, OCH_3), 6.90 (m, 3 H, $-C_6H_3-$); mass spectrum (70 eV) *m/e* (rel intensity) 270 (M^+, 100), 227 (64), 213 (70), 199 (67), 186 (56), 171 (89), 158 (64), 153 (56), 141 (94), 128 (100), 103 (61), 91 (100).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.75; H, 8.00.

No other crystalline compound could be isolated from 50–100% benzene and ether elutes.

Method B. Thermal Decomposition with Copper Sulfate. Thermal decomposition of the diazo ketone **6b** (500 mg, 1.68 mmol) in a mixture of anhydrous tetrahydrofuran (50 ml) and cyclohexane (150 ml) in the presence of anhydrous copper sulfate (2 g) afforded after chromatographic separation 175 mg (38.5%) of the bridged ketone **8b**.

Method C. Decomposition of Crude 6b with Copper Sulfate. When the insertion reaction was carried out with the crude semisolid diazo ketone **6b** in cyclohexane or tetrahydrofuran or a mixture of the two solvents in the presence of anhydrous copper sulfate, the bridged compound **8b** was formed in very low yield (20–25%). The chloro ketone **7b** was also isolated in variable yields (2–7%) from the earlier elutes with petroleum ether–benzene along with the bridged ketone and was separated by fractional crystallization. On recrystallization from ether, the chloro ketone **7b** melted at 151 °C, ir 1720 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}O_2Cl$: C, 70.47; H, 7.50. Found: C, 70.40; H, 7.55.

Hydroxymethylation of 8a. (±)-19,20-Cyclopodocarpa-8,11,13-triene-20-hydroxymethylen-19-one (10a). To an ice-cold stirred suspension of sodium hydride (4 g, 80 mmol of a 50% dispersion) in dry benzene (25 ml) under nitrogen was added a solution of the ketone **8a** (1.3 g, 5.4 mmol) in benzene dropwise followed by the addition of a drop of methanol. After addition of ethyl formate (2.2 ml, 27 mmol), the stirring was continued for an additional 2 h and the solution was left overnight. The excess of sodium hydride was decomposed with a small amount of methanol, diluted with water, acidified with 6 N hydrochloric acid, and extracted with ether. The ethereal layer was extracted with (2%) sodium hydroxide solution. The basic extract was acidified with hydrochloric acid (6 N) and extracted with ether. The ether layer was washed with brine and dried (Na_2SO_4). Evaporation of the solution afforded the hydroxymethylene derivative **10a** (1.2 g, 92%), mp 130–132 °C. Recrystallization from light petroleum furnished the analytical sample: mp 132 °C; ir 1670 and 1600 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.32; H, 7.46.

Oxidation of 10a. (±)-Podocarpa-8,11,13-triene-19,20-dioic Acid (11a). The hydroxymethylene ketone **10a** (1.2 g, 4.5 mmol) was dissolved in sodium hydroxide (100 ml, 10%) and cooled to ca. 10 °C and hydrogen peroxide solution (50 ml, 30%) was added. When the vigor of the reaction subsided, a second lot of alkali solution (50 ml, 10%) was added followed by 30 ml of hydrogen peroxide (30%) and allowed to stand overnight. The reaction mixture was diluted with water and extracted with ether. The aqueous layer was acidified with cold 6 N hydrochloric acid and extracted with ethyl acetate and methylene chloride. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded the dicarboxylic acid **11a** (1.2 g, 93%), mp 234–235 °C dec. The analytical sample was recrystallized from tetrahydrofuran–light petroleum, mp 234–235 °C dec, ir (Nujol) 1700 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.88; H, 7.13.

Methyl ester **12a** (diazomethane method) was recrystallized from light petroleum, mp 135 °C, ir 1725 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.05; H, 7.79.

(±)-20-Carboxypodocarpa-8,11,13-trien-19-oic Acid (13a). A mixture of the hydroxymethylene ketone **10a** (470 mg, 1.8 mmol), glacial acetic acid (7 ml), and powdered hydroxylamine hydrochloride (400 mg, 2.5 mmol) was heated under reflux for 10 min. After cooling to room temperature, a solution of KOH (100 ml, 30% aqueous) was added and refluxed for 60 h. The reaction mixture was diluted with water, acidified with cold 6 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with $NaHCO_3$ solution and the basic extract was chilled and acidified with 6 N HCl. Extraction of the solid with ethyl acetate and evaporation of the solvent afforded the desired acid **13a** (200 mg, 35%), mp 229–230 °C. Recrystallization from ethyl acetate–petroleum ether furnished mp 233 °C, ir (Nujol) 1690 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.29; H, 7.03.

Dimethyl ester **14a** (diazomethane method) was recrystallized from light petroleum: mp 100 °C; ir 1720 cm^{-1}; NMR δ 1.25 (s, 3 H, CH_3), 1.5–2.2 (complex m, 9 H, $-CH_2$ and $-CH<$), 2.31 (br s, 2 H, $-CH_2CO_2Me$), 2.9 (m, 2 H, $-CH_2Ar$), 3.23 (s, 3 H, COOMe), 3.63 (s, 3 H, COOMe), 7.02 (br s, 4 H, ArH).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.81; H, 8.00.

Chromic Acid Oxidation of Bridged Ketone 8a. (±)-19,20-Cyclopodocarpa-8,11,13-triene-7,19-dione (15a). A solution of the ketone **8a** (450 mg, 1.9 mmol) in glacial acetic acid (6 ml) was mixed with a solution of CrO_3 (600 mg, 6 mmol) in water (2 ml) and acetic acid (2 ml) and shaken vigorously for 5–6 min. The reaction mixture was allowed to stand at room temperature overnight and finally heated to 60–65 °C for 2 h. The cooled reaction mixture was diluted with water, saturated with NaCl, and extracted with ether. The ethereal layer was washed with 2% NaOH solution and brine and dried (Na_2SO_4). Evaporation of the solvent left a crystalline residue (360 mg), mp 150–155 °C (ir 1730 and 1680 cm^{-1}), which was chromatographed on neutral alumina (20 g). Elution with petroleum ether afforded the recovered ketone **8a**, mp 114–116 °C (ir 1735 cm^{-1}) (150 mg). Elution with petroleum ether–benzene (1:1) gave the desired diketone **15a**, mp 160–162 °C (160 mg, 50% based on recovered ketone), purified by crystallization from ether–light petroleum: mp 164 °C; ir 1730 and 1680 cm^{-1}; λ_{max} 248 nm (log ϵ 3.98), 287 (3.15); NMR δ 1.08 (s, 3 H), 1.8–2.82 (complex m, 11 H), 7.44 (m, 3 H), 8.02 (m, 1 H).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.06; H, 7.13.

Chromic Acid Oxidation of Diester 12a. (±)-Dimethyl Podocarpa-8,11,13-triene-7-oxo-19,20-dioate (16a). The diester **12a** (400 mg, 1.26 mmol) was dissolved in glacial acetic acid (12 ml) and a solution of chromium trioxide (500 mg, 5 mmol) in water (1.5 ml) and glacial acetic acid (2 ml) was added with vigorous shaking. The reaction mixture was allowed to stand for 20 h with occasional swirling and then heated at 60–65 °C for 20 min. The cooled reaction mixture was diluted with water, saturated with sodium chloride, and extracted repeatedly with ether. The ether layer was washed with 2% sodium hydroxide solution followed by brine and dried (Na_2SO_4). Removal of the solvent afforded a solid (400 mg): mp 110–115 °C; ir 1730 and 1680 cm^{-1}. The material was subjected to chromatography on neutral alumina (15 g). First elution with benzene–petroleum ether (1:9) afforded the recovered diester **12a** (150 mg), mp and mmp 132–134 °C. Elution with benzene–petroleum ether (1:3) yielded the desired keto diester **16a** (200 mg, 77% based on recovered diester). Crystallization from ether–light petroleum afforded the analytical sample: mp 132 °C (mmp with the recovered diester 110–115 °C); ir 1730 and 1680 cm^{-1}; λ_{max} 248 nm (log ϵ 4.05), 285 (3.28).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.22; H, 6.90.

Preparation and Oxidation of 10b to (±)-Podocarpa-8,11,13-triene-13-methoxy-19,20-dioic Acid (11b). Treatment of the bridged ketone **8b** (300 mg, 1.1 mmol) with sodium hydride (1 g, 50%, 20 mmol) and ethyl formate (0.5 ml, 6.2 mmol) in benzene under identical reaction conditions afforded the hydroxymethylene derivative **10b** (235 mg, 70%) as a pink solid: mp 124–126 °C; ir 1670 and 1600 cm^{-1}. Oxidation of this hydroxymethylene derivative (230 mg, 0.77 mmol) with alkaline hydrogen peroxide, exactly under the condition described for the demethoxy analogue, afforded the dicarboxylic acid **11b** (200 mg, 90%), mp 228–230 °C dec, ir (Nujol) 1695 cm^{-1}. The analytical sample (from THF–light petroleum) melted at 232 °C dec.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.90; H, 7.21.

Dimethyl ester **12b** (diazomethane method) was recrystallized from light petroleum, mp 114 °C, ir 1730 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.12; H, 7.60.

Anhydride of 11a (17a). The diacid **11a** (1.2 g, 4.16 mmol) was refluxed with acetyl chloride (40 ml) for 2 h when it gradually went in solution. Removal of excess of the reagent under reduced pressure yielded the crystalline anhydride **17a** (1.10 g, 98%), mp 192–194 °C. Recrystallization from ethyl acetate–petroleum ether afforded the analytical sample: mp 194 °C; ir 1800 and 1760 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.28; H, 6.70.

Anhydride of 11b (17b). The methoxydicarboxylic acid **11b** (200 mg, 0.63 mmol) was refluxed with acetyl chloride (10 ml) for 2 h and then evaporated to dryness under reduced pressure to afford the crystalline anhydride **17b** (180 mg, 95%): mp 167–169 °C; ir 1800 and 1760 cm^{-1}. Recrystallization from ethyl acetate afforded the analytical sample, mp 170 °C.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.80; H, 6.50.

(±)-19,20-Dioxoiminopodocarpa-8,11,13-triene (18a). An intimate mixture of the anhydride **17a** (400 mg, 1.5 mmol) and urea (1 g, 16.7 mmol) was heated at 170–180 °C for 1 h. The solid mass after cooling was broken, treated with water, and filtered. The residue was thoroughly washed with water and dried. Recrystallization from ethyl acetate afforded the desired imide **18a** (380 mg, 95%): mp 248 °C; ir 1720 and 1705 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 75.62; H, 7.41.

(±)-19,20-Dioxoimino-13-methoxypodocarpa-8,11,13-triene (18b). The anhydride **17b** (190 mg, 0.63 mmol) on treatment with urea (500 mg, 8.3 mmol) at 170–180 °C and subsequent purification by crystallization from ethyl acetate afforded the imide **18b** (160 mg, 84%): mp 255 °C; ir 1700 and 1715 cm^{-1}.

Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 72.25; H, 7.22.

(±)-*N*-Acetyl-19,20-iminopodocarpa-8,11,13-triene (1a). To a solution of the imide **18a** (200 mg, 0.74 mmol) in anhydrous diglyme (15 ml) was added lithium aluminum hydride (300 mg, 7.8 mmol) and the mixture was stirred under nitrogen at 50 °C for 30 min and at 100–110 °C for 2 h. A second batch of lithium aluminum hydride (200 mg, 5.3 mmol) was added on cooling to room

temperature and the stirring was continued for another 4 h at 100–110 °C. After keeping overnight at room temperature, the excess of the reagent was destroyed carefully by addition of saturated sodium sulfate solution and then filtered under suction. The residue was thoroughly washed with ether. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of ether afforded a red oil (200 mg) which was immediately dissolved in dry pyridine (4 ml) and acetic anhydride (2 ml) and allowed to stand overnight. The cooled reaction mixture was diluted and acidified with ice-cold 6 N hydrochloric acid and extracted with ether. The ether layer was washed with 2% sodium hydroxide solution followed by brine and dried (Na_2SO_4). Removal of the solvent afforded a gummy solid (200 mg) which was chromatographed on acidic alumina (5 g). Elution with benzene–petroleum ether (3:7) yielded the acetyl derivative **1a**, mp 124–126 °C (160 mg, 76%). Recrystallization from light petroleum afforded the analytically pure specimen: mp and mmp[18] 125–126 °C (lit.[6h] mp 125–126 °C); ir (Nujol) 2920 (s), 2840 (sh), 1635 (s), 1493 (w), 1460 (s), 1440 (sh), 1380 (m), 1365 (m), 1320 (w), 1265 (m), 1050 (w), 1030 (w), 990 (w), and 740 cm^{-1} (m) (comparison[18] ir spectrum with an authentic sample was identical).

Anal. Calcd for $C_{19}H_{25}ON$: C, 80.52; H, 8.89. Found: C, 80.23; H, 8.67.

(±)-*N*-Acetyl-19,20-imino-13-methoxypodocarpa-8,11,13-triene (1b). The imide **18b** (120 mg, 0.4 mmol) in anhydrous diglyme (15 ml) was reduced with lithium aluminum hydride (250 mg, 6.6 mmol) and the product (102 mg) was acetylated with acetic anhydride (1 ml) and dry pyridine (2 ml). After usual work-up, the residue (100 mg) was chromatographed on acid-washed alumina (5 g). Elution with benzene afforded the desired *N*-acetylamine **1b** purified by recrystallization from ether–light petroleum: mp and mmp 165–166 °C (lit.[6e] mp 165–166 °C) (75 mg, 60%); ir (KBr) 1625 (s), 1575 (w), 1500 (m), 1440 (m, broad), 1370 (w), 1270 (s), 1250 (m), 1200 (m), 1160 (w), 1140 (m), 1045 (m), 985 (w), and 810 cm^{-1} (m); GLC on a 4 mm × 2.0 m 1.5% OV-1 on Shimalite W 80–100 mesh at 240 °C showed a single peak with retention time 10.6 min; on a 4 mm × 2.0 m 1.5% OV-17 on Shimalite W 80–100 mesh at 240 °C showed a single peak with retention time 11.7 min (comparative[25] ir spectrum and GLC analyses with an authentic sample[6e] were identical).

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.38; H, 8.72.

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Pyrido[2,3-*d*]pyrimidines. IV. Synthetic Studies Leading to Various Oxopyrido[2,3-*d*]pyrimidines

Arthur D. Broom,* Jaewon L. Shim, and Gary L. Anderson

Department of Biopharmaceutical Sciences, College of Pharmacy, University of Utah, Salt Lake City, Utah 84112

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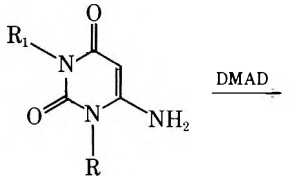
The use of dimethyl acetylenedicarboxylate (DMAD) in protic solvents for the synthesis of a number of new pyrido[2,3-*d*]pyrimidines is described. The structures of the products as 5-carbomethoxy-7-oxopyrido[2,3-*d*]pyrimidines were established by unequivocal synthetic procedures. It was found that a methyl group at N-1 of the starting 6-aminouracils exerts a profound influence on the course of the reaction with DMAD in aprotic solvents to give either C-5 acylation or C-5 alkylation. In protic media, on the other hand, only the products of C-5 alkylation were obtained. Certain mechanistic aspects of the protic vs. aprotic reactions are developed.

Interest has been stimulated in oxo derivatives of pyrido[2,3-*d*]pyrimidines by the observation of significant antitumor activity against Walker muscular carcinosarcoma in rats of 4-oxo- (NSC 112518) and 2,4-dioxopyrido[2,3-*d*]pyrimidine (NSC 112519).[1] Earlier studies directed toward the reactions of dimethyl acetylenedicarboxylate with a number of 6-aminouracil derivatives in aprotic media revealed that all 1-substituted 6-aminouracils studied gave the corresponding 6-amino-5-(3-carbomethoxy-2-propynoyl)uracils rather than the expected pyrido[2,3-*d*]pyrimidines.[2] The object of the present report is to describe similar reactions carried out in protic solvents which do lead to pyrido[2,3-*d*]pyrimidines, to prove the structures of the products, and to consider certain interesting mechanistic aspects of the protic vs. aprotic reactions.

Dimethyl acetylenedicarboxylate (DMAD) has found extensive use in heterocyclic synthesis, both because of its high reactivity and because reaction at the triple bond by either 1,3-dipolar addition[3] or by Michael addition followed by cyclization through the β-ester function[4] provides the double bond requisite to a heteroaromatic system.

Unsubstituted and *N*-methyl derivatives of 6-aminouracil (**1**) provide a particularly interesting case for study, since in addition to the acylation reaction previously described,[2] Michael addition may occur either by attack of C-5 on the triple bond to give **2** after cyclization or by attack of N-6 ultimately yielding **3**.[5]



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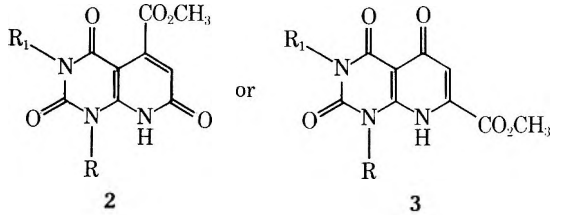
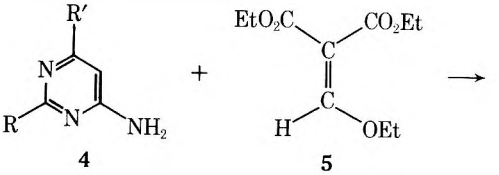


2 or **3**

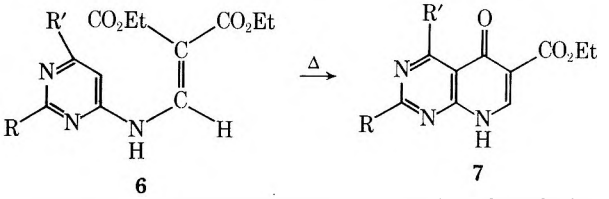
a, R = R_1 = H
b, R = CH_3; R_1 = H
c, R = R_1 = CH_3
d, R = H; R_1 = CH_3

Reaction of 6-amino-1,3-dimethyluracil (**1c**) with DMAD in refluxing methanol gave a 64% yield of a compound readily identifiable as a pyrido[2,3-*d*]pyrimidine by elemental analysis, uv, and ^{1}H NMR spectroscopy. Signals attributable to C-5 H (δ 4.72) and the amino group (δ 6.72) present in **1c** disappeared and the product spectrum consisted of singlets for two *N*-methyl groups (δ 3.48, 3.23), one *O*-methyl (δ 3.85), and C-6 H (δ 6.46). It was necessary to determine, however, which of the two possible isomers **2c** or **3c** was obtained.

A well-known method for the preparation of 5-oxo-6-carbethoxypyrido[2,3-*d*]pyrimidine[6,7] is the Gould–Jacobs reaction, which consists of the reaction of an appropriately substituted 6-aminopyrimidine (e.g., **4**) with diethyl ethoxymethylene malonate (**5**). The intermediate **6** is then thermally cyclized to the 6-carbethoxy-5-oxopyrido[2,3-*d*]-pyrimidine **7** Because intermediates of type **6** are readily characterized by ^{1}H NMR spectroscopy,[6] the structure of the product (**7**) as a 5-oxo rather than a 7-oxo derivative is unequivocally established.



4 **5**

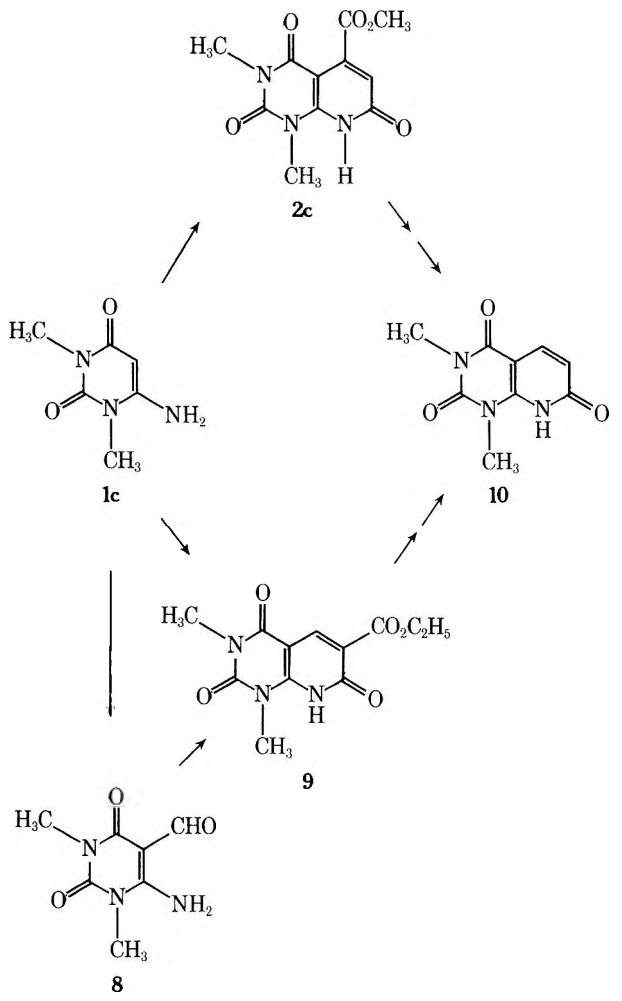


6 **7**

Saponification of **2c** or **3c** followed by decarboxylation would yield, respectively, the 1,3-dimethyl-2,4,7-trioxo- or 1,3-dimethyl-2,4,5-trioxopyrido[2,3-*d*]pyrimidine. It was reasoned that submission of **1c** to the conditions of the Gould–Jacobs reaction should yield 6-carbethoxy-1,3-dimethyl-2,4,5-trioxopyrido[2,3-*d*]pyrimidine which, upon saponification and decarboxylation, should give the 5-oxo isomer and enable by direct comparison the structure assignment of **2c** vs. **3c**. In fact, when this procedure was undertaken, a trioxopyrido[2,3-*d*]pyrimidine identical with the decarboxylated **2c** (**3c**) was obtained, thereby suggesting structure **3c** as correct. However, it was impossible to isolate an intermediate analogous to **6**; either no reaction occurred or only the cyclized material was obtained.

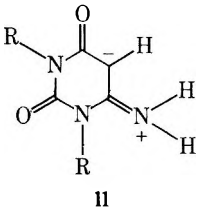
A rigorous proof of structure of the condensation product of **1c** and **5** was therefore undertaken as shown in Scheme I. Condensation of 6-amino-1,3-dimethyl-2,4-dioxo-5-formylpyrimidine (**8**)[8] with diethyl malonate in the presence of piperidine gave unequivocally the 6-carbethoxy-1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**9**), which was found to be identical in every respect with the

Scheme I



reaction product of **1c** and **5** by elemental analysis, uv, ^{1}H NMR, ir, and TLC. These reaction sequences, outlined in Scheme I, conclusively demonstrate that the reaction of **1c** with DMAD yields **2c** rather than **3c** and the saponification and decarboxylation of **2c** and **9** give the 7-oxo derivative **10**.

It is clear that caution must be used in proposing structures by analogy to other reactions; the conversion of **1c** to **9** appears to be the first reported case of carbon alkylation rather than nitrogen alkylation by diethyl ethoxymethylene malonate in the aminopyrimidine series. These reactions emphasize the importance of structural modification on pyrimidine reactivity and suggest that resonance form **11** must play a substantial role in determining C vs. N reactivity.



11

In refluxing aqueous solution DMAD reacted with 1-methyl-6-aminouracil (**1b**) to give 5-carbomethoxy-1-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**2b**). The structure of **2b** was established by the marked similarity of the ^{1}H NMR spectra of **2b** and **2c** and of the uv spectra of the neutral and monoanionic species of both molecules (vide infra). From the reaction of 6-aminouracil (**1a**) under the same conditions only one product (**2a**) was isolated in

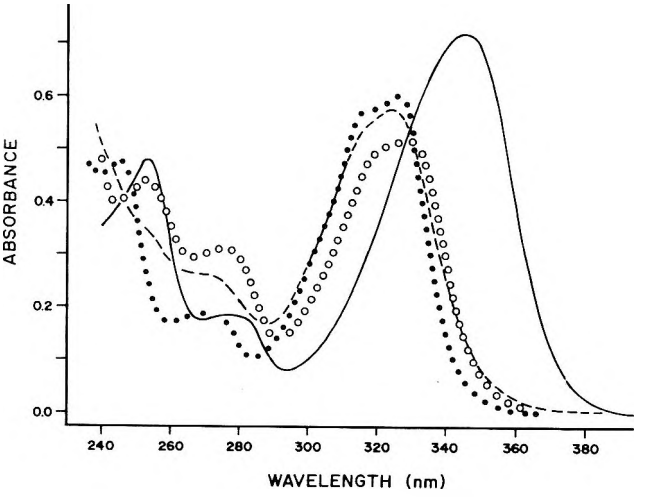
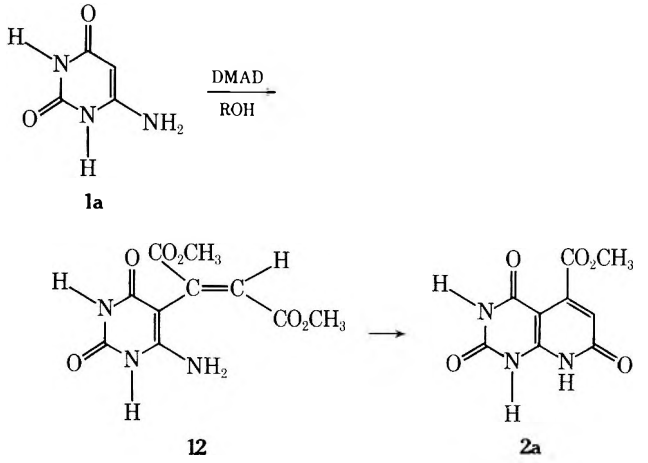


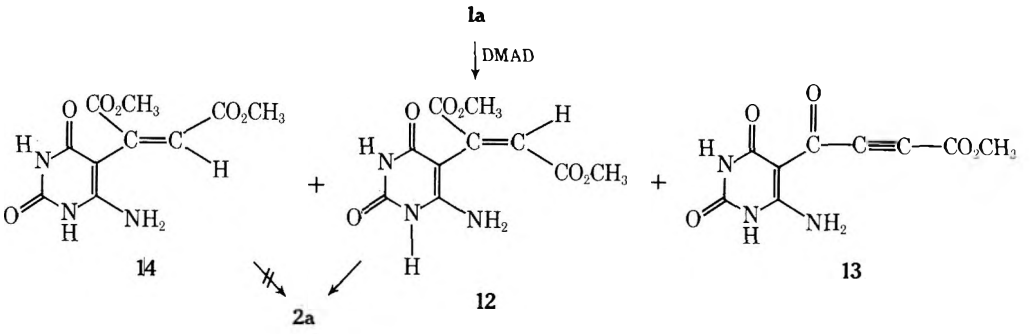
Figure 1. Uv spectra of dianion of **2a** (---), **2b** (●), **2d** (○), and **15** (—).

52% yield. Unequivocal determination of the structure of **2a** was accomplished by carrying out a similar reaction in methanol at room temperature, from which the intermediate fumarate **12** was isolated. Compound **12** was readily



characterized by its ^{1}H NMR spectrum, which consisted of two downfield, D_2O-exchangeable singlets at δ 10.22 and 10.37 corresponding to the ring NH groups, a sharp singlet at δ 6.65 corresponding to the lone fumarate olefinic proton[9] (replacing the C-5 H signal at δ 4.58 in **1a**), a broad, two-proton singlet at δ 6.22 (amino group), and two *O*-methyl signals at δ 3.68 and and 3.65. Upon brief heating in DMF, **12** was quantitatively converted to **2a**.

When DMAD and **1a** were allowed to react in $(CD_3)_2SO$ and the reaction was followed by ^{1}H NMR spectroscopy a different and mechanistically interesting pattern emerged. Three compounds were formed in significant amounts in the approximate ratios of 5:1.5:1. Of the two minor products, the one present in greater quantity was identified as the fumarate derivative (**12**) described above by virtue of the identity of their ^{1}H NMR signals and thin layer chromatographic mobilities. The reaction was run on a larger scale in $(CH_3)_2SO$; the other minor compound was isolated and shown by ^{1}H NMR and elemental analysis to be 6-amino-5-(β-carbomethoxypropynoyl)uracil (**13**). As previously described for the reaction product of **1c** with DMAD in aprotic media,[2] the ^{1}H NMR spectrum of **13** revealed the presence of an *O*-methyl group (δ 3.75) and the loss of the signal for C-5 H. The major product isolated in 41% yield was isomeric to **12** but the olefinic proton signal appeared in the ^{1}H NMR spectrum at δ 5.95 rather than the δ 6.65 signal observed for **12**. When the two isomers

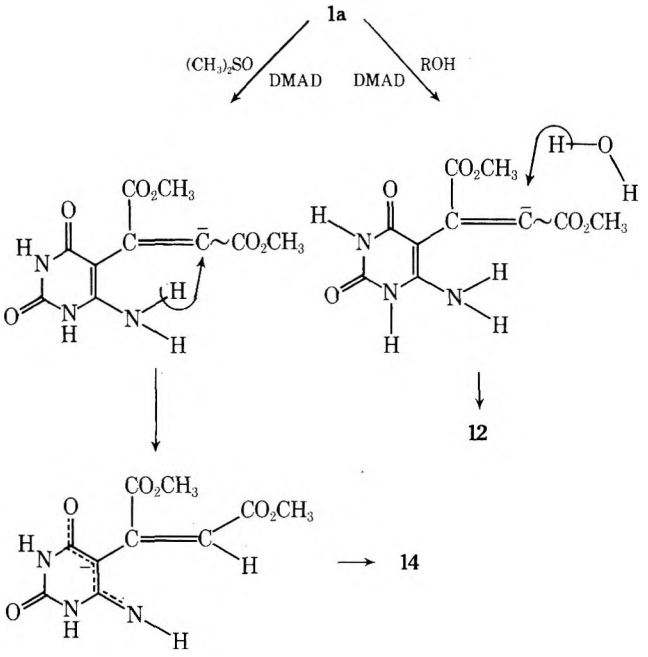


were subjected to heating in DMF compound **12**, as indicated above, readily and quantitatively cyclized to **2a**; under the same conditions **14** underwent no reaction and under forcing conditions gave only a complex mixture of products, thus establishing the stereochemistry of the isomeric olefins.

The solvent dependence of the reaction of 6-aminouracils (**1**) with DMAD is remarkable and only partially understood. There are three major reaction types to consider, i.e., alkylation to give a maleate adduct (e.g., **14**), alkylation yielding a fumarate adduct (e.g., **12**), and acylation to give propynoyl derivatives such as **13**. The reactions appear to be classifiable according to (a) presence or absence of an N-1 substituent and (b) the availability of protons from solvent.

In the absence of a substituent at N-1, for example with **1a**, a 7-oxo-5-carbomethoxypyrido[2,3-*d*]pyrimidine (**2a**) is the major product in water, whereas the maleate adduct **14** predominates in a largely (the solvent was not rigorously dried) aprotic solvent such as $(CH_3)_2SO$. This observation may be readily explained by intramolecular transfer of a proton from the 6-amino group to the Michael anion as illustrated in Scheme II. In water, proton transfer from the solvent shell about the anion presumably permits more rapid formation of the fumarate isomer **12**.

Scheme II



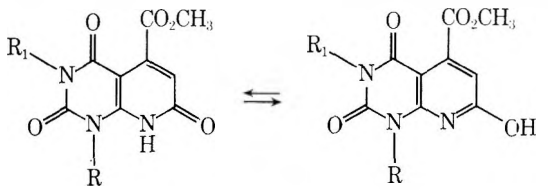
The effect of an N-1 substituent, for example the case of **1c**, is more difficult to understand. In protic media such as water or methanol all the 6-aminouracils are converted by DMAD largely to pyrido[2,3-*d*]pyrimidines **2**. In aprotic media, however, the presence of an N-1 substituent causes acylation to occur essentially to the exclusion of alkylation, in sharp contrast to the reaction of **1a** in which the acylation product comprises only about 15% of the reaction mixture. This appears to be a unique phenomenon which has considerable importance in determining optimum conditions for the use of DMAD in synthetic heterocyclic chemistry. It is being intensively studied at this time and will be the subject of a further report in the near future.

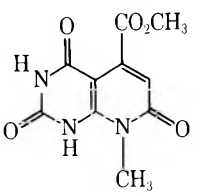
It was of interest to determine whether pyrido[2,3-*d*]pyrimidines bearing a 7-oxo group as the only pyridine ring substituent could be obtained directly rather than through the low-yield decarboxylation procedure described above. It was determined that the reaction of **1c** with ethyl propiolate in refluxing water did indeed give a good yield of **10** directly, identical in all respects with the products obtained from the decarboxylation of **2c** and **9**.

It has been widely assumed in heterocyclic chemistry that substitution of methyl for hydrogen in a heteroaromatic lactam system results in little change in the uv spectrum; numerous examples have been cited[10] using *N*-methyl and *O*-methyl derivatives to show that α- and γ-oxo N-heteroaromatic molecules exist in the lactam (oxo) form. It was, therefore, somewhat surprising to find substantial differences between the uv spectra of the neutral forms of 1-methyl derivatives **2b** and **2c** on the one hand and those of **2a** and **2d** on the other; the latter should have a proton at N-1 in the neutral form. A more detailed examination of the spectra was undertaken in order to understand this anomaly.

Determination of the pK_a values for **2a** and **2d** revealed no significant differences for either the first or second ionizations, suggesting that the first ionization in all four compounds occurs from N-8. As noted above, the spectra of the monoanions of the two 1-methyl derivatives **2b** and **2c** are virtually identical, as are those of **2a** and **2d**. One might suggest, therefore, that the spectral differences between the two pairs arise from initial ionization of N-1 from **2a** and **2d**. This possibility was excluded, however, by examination of the dianion spectra (Figure 1) in which the dianion of **2a** much more closely resembles that of the 1-methyl derivative **2b** than that of the 3-methyl derivative **2d**.

The most likely alternative explanation for the spectral difference is a difference in tautomeric structure of the 7-oxo (hydroxy) function in **2a, 2d** vs. **2b, 2c**. Two additional compounds were synthesized; 5-carbomethoxy-8-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**15**) was made from the reaction of 6-methylaminouracil and DMAD and 5-carbomethoxy-7-methoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-





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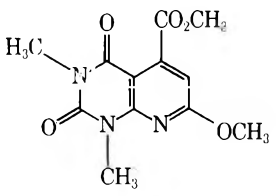

16

d]pyrimidine (**16**) was prepared by the methylation of **2c** with diazomethane. Compound **16** was shown to be an *O*-methyl rather than an *N*-methyl derivative by its ^{1}H NMR spectrum; the newly formed *O*-methyl substituent resonated at δ 3.97 vs. δ 3.53 for the 8-*N*-methyl derivative. The proton signal for C-6 of **16** appeared at δ 6.70, downfield 0.53 ppm from the C-6 H of **15**, as would be expected from the increase in ring current resulting from the "aromatization" of the system. Final confirmation of the structure was obtained by the conversion of **2c** to the 7-chloro derivative **17** with $POCl_3$–PCl_5. Reaction of **17** with methoxide gave **16**. That chlorination had occurred at the 7 position was confirmed by the catalytic dehalogenation of **17** to give 5-carbomethoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (**18**); the presence in the ^{1}H NMR spectrum of a pair of doublets ($J_{6,7}$ = 4.8 Hz) is compatible only with **18**.[9]

Comparison of the uv spectra (Figure 2) of these "locked" lactam and lactim (**16**) tautomers with those of representative derivatives **2a** (unmethylated) and **2c** (1,3-dimethyl) suggests strongly that the influence of a methyl group at N-1 is to increase the proportion of lactim (hydroxy) tautomer of the C-7:N-8 tautomeric function. Such a finding suggests that a note of caution is in order in the frequently made assumption that substitution of O=CNCH$_3$ for O=CNH– in heteroaromatic system will have no effect on the uv spectrum.

Experimental Section

^{1}H NMR spectra were obtained on a Jeolco C-60H spectrometer using $(CD_3)_2SO$ as a solvent with DSS as an internal standard. Uv spectra were run on a Cary 15 spectrophotometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. pK_a values were determined spectrophotometrically according to Albert.[11]

5-Carbomethoxy-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2a). Compound **1a** (640 mg, 5 mmol) was refluxed with DMAD (900 mg, 6 mmol) in H_2O (30 ml) for 4 h. The suspension was filtered hot to give 626 mg (52%) of **2a**. Recrystallization twice from DMF–$2H_2O$ afforded 188 mg: mp 320 °C dec; uv (pH 1) 312 nm (ϵ 13 060), 275 (9750), (pH 7) 322 (14 430), 279 (9980), (pH 14) 324 (14 280), 270 (7070); ^{1}H NMR δ 11.27 (s, 1, NH), 6.35 (s, 1, CH), 3.87 (s, 3, OCH_3); pK_{a1} = 4.5 ± 1, pK_{a2} = 10.9 ± 1.

Anal. Calcd for $C_9H_7N_3O_5$: C, 45.57; H, 2.95; N, 17.72. Found: C, 45.55; H, 2.95; N, 17.76.

5-Carbomethoxy-1-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2b). Compound **1b** (700 mg, 5 mmol) was refluxed with DMAD (900 mg, 6 mmol) in H_2O (30 ml) for 50 min. The clear yellow-orange solution was cooled to room temperature to give a heavy precipitate which was filtered and recrystallized from EtOH–H_2O (1:1) to yield 600 mg of pure product. Additional product (200 mg) was obtained from the filtrate. Total product, 800 mg (64%), was dissolved in hot EtOH, treated with charcoal, filtered, and evaporated to give 477 mg (38%) of **2b**: mp 289 °C dec; uv (pH 1) 314 nm (ϵ 12 050), 283 (sh), 263 (6980), (pH 7) 322 (16 200), 312 (16 300), 275 (8740), (pH 14) 328 (13 400), 275 (8600), 253 (12 000); ^{1}H NMR δ 11.50 (s, 1, NH), 6.45 (s, 1, CH), 3.85 (s, 3, OCH_3), 3.45 (s, 3, NCH_3); pK_{a1} = 4.6 ± 0.1, pK_{a2} = 11.3 ± 0.1.

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 47.57; H, 3.55; N, 17.11.

5-Carbomethoxy-1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2c). Compound **1c** (1.55 g, 10 mmol) was refluxed with DMAD (1.56 g, 11 mmol) in MeOH (50 ml) for 26 h. The reaction mixture was filtered hot, and the filtrate condensed to a small volume. The solid was filtered and recrystallized from MeOH to give 1.69 g (64%) of **2c**: mp 239–240 °C;[12] uv (pH 1) 315 nm (ϵ 14 100), 278 (9750), 262 (11 100), (pH 7) 323 (19 200), 313 (19 300), 273 (12 000), (pH 11) 322 (19 200), 312 (19 300), 273 (11 900); ^{1}H NMR δ 6.47 (s, 1, CH), 3.85 (s, 3, OCH_3), 3.48 (s, 3, NCH_3), 3.23 (s, 3, NCH_3); pK_{a1} = 4.6 ± 0.1, pK_{a2} = 11.3 ± 0.1.

Anal. Calcd for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.75; H, 4.15; N, 15.89.

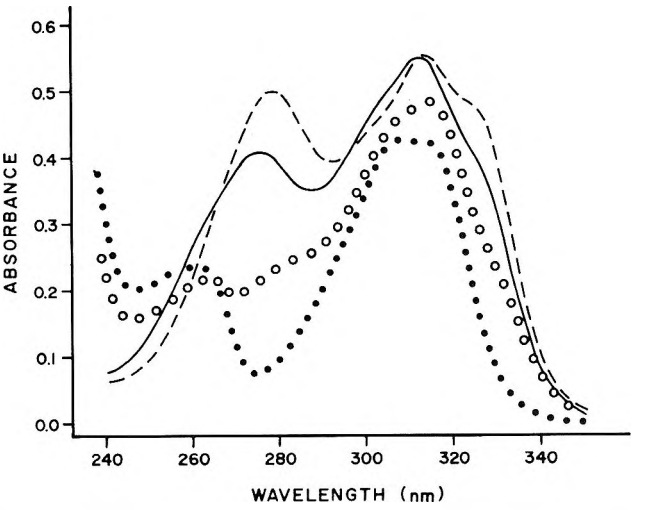

Figure 2. Uv spectra of neutral molecule of **2a** (—), **2c** (O), **15** (---), and **16** (●).

5-Carbomethoxy-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2d). Compound **1d** (705 mg, 5 mmol) was refluxed with DMAD (740 mg, 5.2 mmol) in H_2O (40 ml) for 3 h. The precipitate which formed was filtered to give a pink powder, which was dissolved in hot DMF–H_2O and treated with charcoal twice, and the filtrate was cooled to room temperature. The white crystals were filtered to give 546 mg (44%) of **2d**: mp 317–319 °C dec; uv (pH 1) 313 nm (ϵ 14 100), 275 (8300), (pH 7) 323 (15 300), 297 (9100), (pH 14) 326 (15 600), 268 (5700), 245 (13 000); ^{1}H NMR δ 6.40 (s, 1, CH), 3.73 (s, 3, OCH_3), 3.25 (s, 3, NCH_3); pK_a = 4.5 ± 0.1.

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 48.03; H, 3.53; N, 16.52.

6-Carbethoxy-1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (9). Method A. Compound 8[8] (550 mg, 3 mmol), piperidine (0.25 ml, 2.5 mmol), and diethyl malonate (1.5, 9.9 mmol) were refluxed in EtOH (20 ml) for 24 h. Diethyl malonate (1.0 ml, 6.6 mmol) was added and refluxing was continued for 48 h. The precipitate which formed on cooling was filtered to give 320 mg (42%) of white crystals. Recrystallization from dilute HCl (pH 2), then H_2O gave analytically pure sample: mp 196–170 °C; uv (pH 1) 317 nm (ϵ 21 200), 276 (14 300), (pH 7) 331 (25 100), 283 (18 200), (pH 11) 331 (24 700), 283 (17 800); ^{1}H NMR δ 8.33 (s, 1, CH), 4.27 (q, 2, CH_2), 3.43 (s, 3, NCH_3), 3.22 (s, 3, NCH_3), 1.33 (t, 3, CH_3).

Anal. Calcd for $C_{12}H_{13}N_3O_5 \cdot 0.5H_2O$: C, 49.95; H, 4.85; N, 14.58. Found: C, 50.05: H, 5.19; N, 14.47.

Method B. Compounds **1c** (1.55 g, 10 mmol) and **5** (2.35 g, 11 mmol) were fused at an oil bath temperature of 210 °C. After cooling to room temperature, the melt was dissolved in 200 ml of $CHCl_3$, treated with charcoal, and filtered. The filtrate was reduced to a volume of 20 ml and the product precipitated by the addition of EtOH (200 ml). The solid was filtered and recrystallized from $CHCl_3$–MeOH to give 0.80 g (29%) of **9**: melting point, uv, ^{1}H NMR, and TLC were identical with those of compound prepared by method A.

Anal. Calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.66; N, 15.05. Found: C, 51.52; H, 4.66; H, 14.94.

1,3-Dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (10). Method A. Compound **2c** (5 g, 19 mmol) was refluxed in H_2O (50 ml) containing NaOH (1.5 g, 37.5 mmol) for 8 h. The cooled reaction mixture was neutralized with dilute HCl. The precipitate was filtered and washed with H_2O to give 4 g (85%) of 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxylic acid: mp 320 °C; uv (pH 1) 312 nm (ϵ 12 400), 281 (sh), 263 (5980), (pH 7) 316 (17 700), 307 (18 000), 274 (7720), (pH 11) 316 (18 200), 307 (18 300), 274 (7720); ^{1}H NMR δ 6.47 (s, 1, CH), 3.53 (s, 3, NCH_3), 3.28 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 47.99; H, 3.69: N, 16.68.

This acid (4 g, 15.9 mmol) was heated at 330–350 °C in a vacuum sublimator for 2 h. The sublimate was triturated with EtOAc

and filtered. The filtered product was triturated with MeOH, filtered, and dried to give 216 mg (7%) of **10:** mp 274–275 °C; uv (pH 1) 311 nm (ε 13 750), 306 (sh), 281 (sh), 265 (sh), (pH 7) 321 (18 250); 308 (20 140), 274 (7700), (pH 11) 321 (18 670), 308 (20 350), 274 (7760); ^{1}H NMR δ 7.93 (d, 1, C-5 H, $J_{5,6}$ = 8.1 Hz), 6.42 (d, 1, C-6 H, $J_{5,6}$ = 8.1 Hz), 3.45 (s, 3, NCH_3), 3.21 (s, 3, NCH_3).

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.08; H, 4.43; H, 20.05.

Method B. Compounds **9** (3.5 g, 12.5 mmol) was refluxed in H_2O (50 ml) containing NaOH (1.5 g, 37.5 mmol) for 8 h. The solution was filtered and the filtrate was neutralized with dilute HCl to pH 7. The fine crystals which formed were filtered and triturated with methanol and with water to yield 3 g (94%) of 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid: mp > 320 °C; ^{1}H NMR δ 8.32 (s, 1, CH), 3.42 (s, 3, NCH_3), 3.22 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 47.78; H, 3.60; N, 16.59.

This acid (2 g, 8.0 mmol) was treated as in method A to give 60 mg (4%) of **10**, identical by TLC, uv, ^{1}H NMR, and melting point with **10** from method A.

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.12; N, 4.37; N, 20.19.

Method C. Compound **1c** (455 mg, 3 mmol) and ethyl propiolate (0.40 ml, 4 mmol) were refluxed in H_2O (20 ml) for 24 h. The suspension was cooled and filtered to give 427 mg (69%) of **10.** Recrystallization from MeOH gave **10** identical by TLC, uv, ^{1}H NMR, and melting point with **10** from method A.

Dimethyl-2-(6-amino-2,4-dioxo-5-pyrimidinyl)fumaric Acid (12). Compound **1a** (640 mg, 5 mmol) and DMAD (900 mg, 6 mmol) were stirred in MeOH for 5 days. The filtrate was evaporated to dryness with EtOH twice, then triturated thoroughly with Et_2O and filtered to give 555 mg (41%) of **12.** For analysis, the solid was dissolved in EtOH, treated with charcoal, and filtered, and the filtrate allowed to stand at room temperature for several days. The crystals were filtered, washed with EtOH and dried: mp 225 °C dec; uv (pH 1) 312 nm (ε 11 400), 269 (11 100), (pH 7) 322 (14 500), 279 (10 000), (pH 11) 322 (14 500), 273 (8340), 228 (17 200); ^{1}H NMR δ 10.37 (s, 1, NH), 10.22 (s, 1, NH), 6.65 (s, 1, CH), 6.22 (s, 2, NH_2), 3.68 (s, 3, OCH_3), 3.65 (s, 3, OCH_3).

Anal. Calcd for $C_{10}H_{11}N_3O_6{\cdot}0.5H_2O$: C, 43.15; H, 4.35; N, 15.11. Found: C, 43.23; H, 4.40; N, 15.19.

Conversion of 12 to 2a. **12** (40 mg) was heated in DMF at 150 °C for 30 min. Evaporation of DMF gave only a compound identical by tlc and ^{1}H NMR with **2a.**

6-Amino-5-(3-carbomethoxy-2-propynoyl)uracil (13) and Dimethyl-2-(6-amino-2,4-dioxo-5-pyrimidinyl)maleic Acid (14). Compound **1a** (1.0 g, 7.87 mmol) was dissolved in Me_2SO (15 ml). DMAD (1.16 g, 8.13 mmol) was added and the solution stirred overnight. MeOH (75 ml) was added and the solution stored at 5 °C for 24 h. The yellow crystals were filtered to give 113 mg of **13** (5.8%). To the filtrate was added 400 ml of Et_2O and the yellow solution stored at 5 °C for 2 days. Filtration afforded 918 mg (40.8%) of **14.** For analysis **13** was recrystallized from DMF–H_2O: mp <310 °C (slowly darkens); uv (pH 1) 427 nm (ε 9200), 276 (14 400), 262 (sh), (pH 7) 333 (23 500), 273 (10 000), (pH 11) 333 (24 700), 273 (9300); ^{1}H NMR δ 10.08 (br, 4, NH_2, NH, NH), 3.75 (s, 3, CH_3).

Anal. Calcd for $C_9H_7N_3O_5{\cdot}0.5H_2O$: C, 43.90; H, 3.25; N, 17.07. Found: C, 43.99; H, 3.31; N, 16.99.

Recrystallization of **14** by dissolving in 350 ml of MeOH at 25 °C, followed by evaporation in vacuo to ~100 ml and then addition of 200 ml of Et_2O, gave 636 mg (28%) of pure compound: mp 195 °C effervescence (slowly decomposed); uv (pH 1) 328 nm (ε 7400), 267 (14 400), (pH 7) 338 (6400), 267 (12 900), (pH 11) 388 (4700), 271 (16 500); ^{1}H NMR δ 10.55 (s, 1, NH), 10.30 (s, 1, NH), 6.65 (s, 2, NH_2), 5.95 (s, 1, CH), 3.65 (s, 6, OCH_3).

Anal. Calcd for $C_{10}H_{11}N_3O_6{\cdot}H_2O$: C, 41.81; H, 4.53; N, 14.63. Found: C, 41.84; H, 4.72; N, 14.96.

5-Carbomethoxy-8-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (15). DMAD (575 mg, 4 mmol) and 6-methylaminouracil[13] (423 mg, 3 mmol) were refluxed in H_2O (30 ml) for 1 h. The hot solution was filtered through charcoal and the filtrate cooled overnight to give 261 mg (35%) of **15** after filtration. An analytical sample was recrystallized from EtOH–H_2O which decomposed at >305 °C: uv (pH 1) 313 nm (ε 13 300), 279 (12 050), (pH 7) 335 (14 900), 284 (11 100), (pH 14) 345 (18 000), 279 (14 600), 253 (12 000); ^{1}H NMR δ 11.50 (s, 1, NH), 6.17 (s, 1, CH), 3.83 (s, 3, OCH_3), 3.53 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.61; N, 16.72. Found: C, 47.89; H, 3.84; N, 16.44.

5-Carbomethoxy-7-methoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (16). Method A. Compound **2c** (500 mg, 1.9 mmol) was dissolved in methanol (75 ml) with stirring. To the clear solution was added 40 ml of diazomethane–ether solution portionwise until the yellow color was maintained for 1 h. After evaporation in vacuo, the residue was recrystallized from EtOH to give 450 mg (86%) of **16:** mp 154–155 °C; uv (pH 1) 307 nm (br) (ε 11 800), 261 (7300), (pH 7) 207 (br) (12 000), 261 (7200), (pH 11) 307 (br) (12 000), 261 (7300); ^{1}H NMR δ 6.70 (s, 1, CH), 3.97 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.50 (s, 3, NCH_3), 3.20 (s, 3, NCH_3).

Anal. Calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.66; N, 15.05. Found: C, 51.67; H, 4.81; N, 15.25.

Method B. To MeOH (3 ml) containing Na (70 mg) was added **17** (100 mg, 0.35 mmol). After stirring for 1 h, H_2O (2 ml) was added and the pH adjusted to 7 with HOAc. Filtration afforded 85 mg (86%) of **16,** identical by TLC, uv, ^{1}H NMR, and melting point with **16** from method A.

5-Carbomethoxy-7-chloro-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (17). Compound **2c** (2.65 g, 10 mmol) was refluxed in $POCl_3$ (50 ml) containing PCl_5 (2.3 g, 11 mmol) for 3 h. Excess $POCl_3$ was removed in vacuo, and the residue was stirred with 150 g of ice for 15 min, then extracted with $CHCl_3$ (3 × 125 ml). The $CHCl_3$ was extracted with ice–H_2O three times and dried over $MgSO_4$. This was evaporated to about 10 ml, 50 ml of petroleum ether was added, and the solid was filtered. The filtrate was evaporated and triturated with ether to give a white solid (937 mg) of nearly pure **17.** The product was used for the synthesis of **16** and **18** without further purification: ^{1}H NMR δ 7.52 (s, 1, CH), 3.87 (s, 3, OCH_3), 3.50 (s, 3, NCH_3), 3.25 (s, 3, NCH_3).

5-Carbomethoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (18). Compound **17** (500 mg, 1.76 mmol) was dissolved in 1,2-dimethoxyethane (100 ml) in which Pd/C 10% (200 mg) and NaOAc (145 mg, 3.5 mmol) were suspended. This was shaken under H_2 (42 psi) for 36 h. Filtration through Celite, followed by evaporation in vacuo, gave an oily solid which was dissolved in boiling EtOH (20 ml). Cooling to room temperature gave 246 mg of **18** (56%): mp 153–155 °C; uv (pH 1) 315 nm (ε 6300), 248 (sh), (pH 7) 315 (6700), 248 (sh), (pH 11) 315 (6100), 248 (sh); ^{1}H NMR δ 8.70 (d, 1, C_7 H), 7.23 (d, 1, C_6 H) ($J_{6,7}$ = 4.8 Hz), 3.82 (s, 3, OCH_3), 3.50 (s, 3, NCH_3), 3.22 (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{11}N_3O_4{\cdot}0.5H_2O$: C, 51.16; H, 4.68; N, 16.30. Found: C, 51.05; H, 4.68; N, 16.37.

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Registry No.—**1a,** 873-83-6; **1b,** 2434-53-9; **1c,** 6642-31-5; **1d,** 2236-97-5; **2a,** 57821-16-6; **2b,** 57821-17-7; **2c,** 37587-38-5; **2d,** 57821-18-8; **5,** 87-13-8; **8,** 54660-80-9; **9,** 57821-19-9; **10,** 57821-20-2; **12,** 57821-21-3; **13,** 57821-22-4; **14,** 57821-23-5; **15,** 57821-24-6; **16,** 57821-25-7; **17,** 57821-26-8; **18,** 57821-27-9; DMAD, 762-42-5; diethyl malonate, 105-53-3; 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxylic acid, 57821-28-0; 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid, 57842-79-2; ethyl propiolate, 623-47-2; 6-methylaminouracil, 34284-87-2; diazomethane, 334-88-3; MeOH, 67-56-1.

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Reactions of the Derivatives of 5-Bromopyrimidine Nucleosides with Sodium Azide

Tadashi Sasaki,* Katsumaro Minamoto, Mitsuhiko Kino, and Takehisa Mizuno

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

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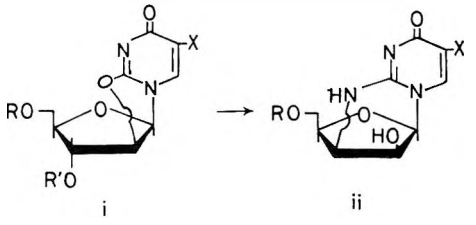
To exploit azide chemistry in the nucleoside field, protected 5-bromopyrimidine nucleosides were synthesized as substrates for the reaction of azide ion. These include 2′,3′-*O*-isopropylidene-5′-*O*-benzoyl- and -5′-*O*-tosyl-5-bromouridine (**2a** and **2b**), 2′,3′-*O*-anisylidene-5′-*O*-benzoyl-5-bromouridine (**2c**), and 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-5-bromocytidine (**11**). **2a,b** with sodium azide yielded the same compound, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (**3a**), while a similar reaction with **2c** gave the corresponding 2′,3′-*O*-anisylidene analogue (**3b**). Acidic hydrolysis of **3a,b** gave 9,5′-cyclo-3-β-D-ribofuranosyl-8-azaxanthine (**4**). **11** with sodium azide gave 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromocytidine (**12**) and 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**). **3a** and **13** were also obtained merely by heating 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**6**) and **12**, respectively, suggesting an intramolecular addition–elimination mechanism for the formations of **3a,b** and **13**. Hydrazinolysis of **3a** gave N^1,5′-anhydro-N^5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-carboxyhydrazino-5-amino-υ-triazole (**9**).

Azides exhibit many aspects of reactivity which can lead to amines, imines, nitrenes, and triazoles depending upon reaction conditions and the character of the substrate,[1] although their principal use in the nucleoside area has been limited to the syntheses of amino sugar nucleosides more or less related to natural products.[2,3] Recently we reported a selective, one-step synthesis of derivatives (ii) of 2,3′-imino-1-(β-D-lyxofuranosyl)uracil from readily available 2,2′-anhydro uracil arabinosides (i) and azide ion.[4] This reaction involves the leaving group directed, selective attack of azide ion at C-2 followed by intramolecular nucleophilic displacement at C-3′ with release of a nitrogen molecule.

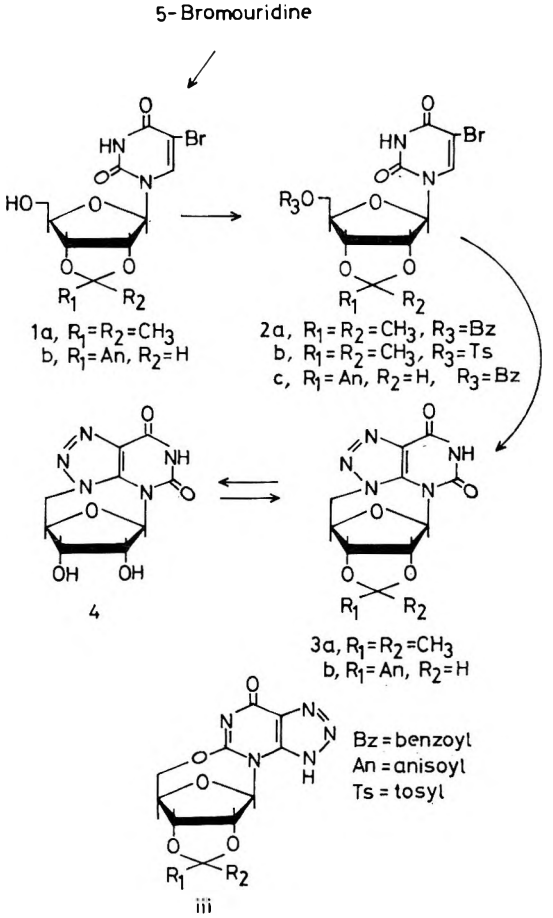


R = H, benzoyl or trityl
R′ = tosyl or mesyl
X = H or Br

Our attention was directed next to the possible interaction between 5′ carbon and an azide group introduced at C-6 when an appropriate leaving group is present at C-5′. The readily available 5-bromopyrimidine nucleoside derivatives seemed to be convenient substrates for such an investigation; some of the 5-halopyrimidine nucleosides are known to be chemicals of biological interest and vulnerable to the attack of some nucleophiles at the 5,6 double bond in the sense of nucleophilic addition reactions.[5] A few complex and hence interesting situations were foreseen for the present investigation: (a) the initial attack of azide ion could occur either at C-5′ or C-6, (b) the introduced azide group could induce intramolecular reactions with or without decomposition of the nitrogen chain, and (c) the possible interaction between the C-6 azide and 5′ carbon could take a concerted or limited course since the formation of a 5,6-fused triazole is highly possible. This paper describes the results of a synthetic study carried out on the basis of the above considerations.

2′,3′-*O*-Isopropylidene-5-bromouridine (**1a**)[6] and 2′,3′-*O*-anisylidene-5-bromouridine (**1b**)[7] were prepared by known methods. In the first experiment, **1a** was treated with excess sodium azide to observe the reactivity of the base moiety, but gave an intractable complex mixture. Hence, 5′-*O*-benzoyl-2′,3′-*O*-isopropylidene-5-bromouridine (**2a**) was used to preclude possible participation by the 5′-hydroxyl group, in the expectation that a 5,6-υ-triazolopyrimidine nucleoside retaining the protecting group at C-5′ would be formed exclusively since similar reactions of 5-nitropyrimidines as well as their nucleoside derivatives with sodium azide have been documented.[8,9]

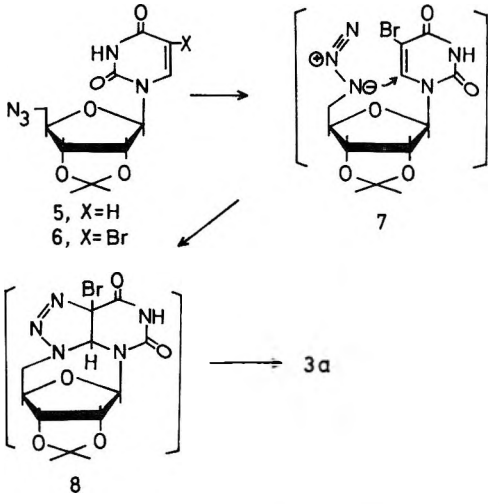
Reaction of **2a** with excess sodium azide in *N,N*-dimethylformamide (DMF) at 110 °C gave, unexpectedly, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (**3a**) as the only product in 70% yield. The same compound was also formed in a similar but shorter time reaction from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-5-bromouri-



dine (**2b**). Its analysis (empirical formula $C_{12}H_{13}N_5O_5$) and mass spectroscopic data (M^+ *m/e* 307) showed the incorporation of an azide unit as such and the elimination of the 5′-benzoyloxy or tosyloxy group. This substance showed no azide absorption in the ir spectrum and no NMR signals for pyrimidine 5 and 6 protons and hence must be a triazole derivative fused at the 5 and 6 positions of the base. Nuclear magnetic resonance spectroscopy (vide infra) gave no conclusive structural informations at this stage.

Since compound **3a** tended to be partially hydrated during crystallization and rendered the analysis rather cumbersome, 5′-*O*-benzoyl-2′,3′-*O*-anisylidene-5-bromouridine (**2c**) was also prepared and submitted to a similar azide reaction, yielding highly characterizable crystals of 9,5′-cyclo-3-(2′,3′-*O*-anisylidene-β-D-ribofuranosyl)-8-azaxanthine (**3b**). Compounds **3a** and **3b** gave similar uv absorption patterns with maxima at around 230 and 255 nm except that intensity order of the two maxima in **3b** was reversed owing to the presence of the anisoyl and were deprotected to the same, single product, 9,5′-cyclo-3-β-D-ribofuranosyl-8-azaxanthine (**4**), which was obtained both in the form of its methanol solvate and as solvent-free crystals. Compound **4** absorbed at 240 and 257 nm and could be reconverted to **3a**. However, the above data were not sufficient to rule out another possible structure, iii, in which the 2 oxygen is bound to the 5′ methylene, as long as no literature analogue was available for direct uv spectral comparison.

Accordingly, an unambiguous synthesis of **3a** was attempted. 5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**5**)[10] was treated with *N*-bromoacetamide to give 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**6**), which on heating in DMF at 110–120 °C afforded **3a** in a high yield (crude yield: quantitative). This intramolecular thermal reaction must have proceeded via nucleophilic addition of the azide group followed by elimination of the elements of hydrogen bromide as in the formation of 5,6-anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine[5a] or of a 6-cyanouridine derivative[5b] from **1a** by the action of alkali or cyanide ion.

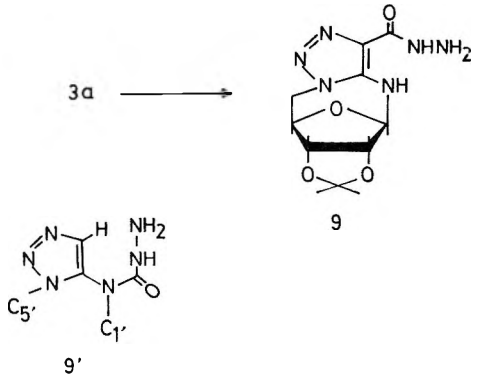


At this point, some comments on the unusual features of the NMR spectra of **3a** and **4** are in order[11] (see Experimental Section). In the 100-MHz spectrum of **3a** there appeared widely separated, well-resolved $H_{5'a}$ (doublet, J_{gem} = 12 Hz) and $H_{5'b}$ signals (doublet of doublets, J_{gem} = 12 Hz, $J_{4',5'b}$ = 4.5 Hz) at 5.16 and 4.60 ppm, respectively. We are not aware of values as low as 5.16 ppm for the chemical shifts of the 5′-methylene protons of a nucleoside derivative. O^2-5′-[12] and 6,5′-cycloprimidine nucleosides[13] are known to show highly nonequivalent 5′ protons between 3.88 and 4.73 ppm. As an example of *N*,5′-cyclonucleosides, 2′,3′-*O*-isopropylidene-N^2,5′-cycloisocytidine[14] shows 5′-proton signals at 3.17 and 3.40 ppm as a set of doublets with J_{gem} = 13.8 Hz.[14] N substitution at a heterocyclic ring would, admittedly, be expected to shift the 5′-proton signals to lower field as compared with an imino bridged 5′-cyclonucleoside. Inspection of a molecular model of **3a** in the endo conformation (with the N^9 lone pair lying over the furanose ring and the N^3 lone pair over the $C_{1'}$–$C_{2'}$ bond) has shown that one of the 5′-methylene protons with a dihedral angle of approximately 90° can take a position coplanar with the triazole ring (deshielding zone), while the other lies in the vicinity of its shielding zone. Thus, the influence of the triazole ring current seems to be responsible for the unusually low, widely separated chemical shifts of the 5′ protons. On the other hand, an exo conformer requires dihedral angles of 0 and 120° between $H_{4'}$ and $H_{5'}$ and hence is improbable.[15] Overlap of $H_{2'}$ and $H_{3'}$ signals is also found in 2′,3′-*O*-isopropylidene-O^2,5′-cyclouridine.[12]

The deprotected analogue, **4**, also showed similar patterns for the 5′ protons (see Experimental Section). A notable difference from **3a** is the separation of the resonances of $H_{2'}$, $H_{3'}$, and $H_{4'}$, the last being significantly shifted upfield. The reason for the apparition of $H_{2'}$ and $H_{3'}$ signals as a rather ill-defined quartet and quintet is uncertain at present.[16] However, the homogeneity of **4** and the skeletal identity with **3a** are evident from the appearance of the signals of the other sugar protons and the reconversion into **3a** (vide supra).

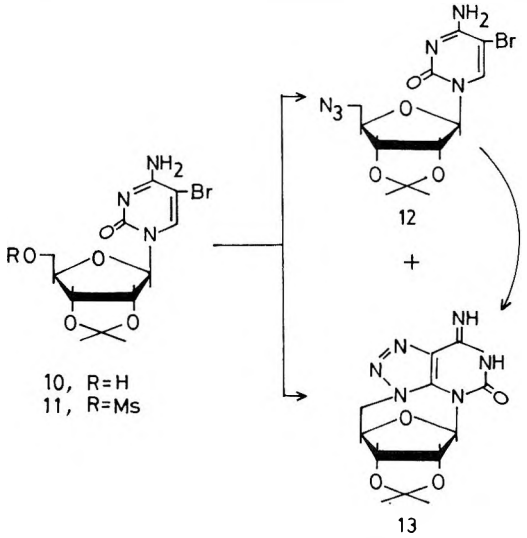
Thus, while some uncertainty attended the interpretations of the irregular resonances of **4**, the structures of **3** and **4** were firmly established by the thermal conversion of **6** into **3a**.

Prior to this cyclization experiment, a few degradation reactions were carried out to obtain some structural information. Heating **4** in 3 N hydrochloric acid at 95–100 °C for 12 h resulted in complete recovery of **4**, while heating **3a** in 1 N sodium hydroxide at 60–70 °C for 24 h revealed a slow and complex degradation, but no products were isolated. On the other hand, brief treatment of **3a** with 85% hydrazine allowed isolation of a homogeneous crystalline product which absorbed at 238 and 259 nm (sh). Analysis and mass spectroscopic data (see Experimental Section) indicated the incorporation of a molecule of hydrazine with expulsion of a –NHC=O unit (probably as carbamic acid). These data seem to be sufficient to assign to this compound the structure of N^1,5′-anhydro-N^5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-carboxyhydrazino-5-amino-υ-triazole (**9**) since genesis of another partial structure, **9′**, arising by fission of the triazole-conjugated carbonyl, is highly improbable under the mild reaction conditions. This hydrazide also presented some unusual features in the NMR spectrum[11] (see Experimental Section). Resonances of the 5′ methylene appeared at 4.12 and 4.94 ppm as a set of



clear-cut doublets of doublets with J_{gem} = 14 and $J_{4',5'a}$ = $J_{4',5'b}$ = 2.3 Hz. These chemical shifts are comparable with those of **3a** and **4** and suggest that the triazole ring and N¹,5′ bonding are present intact. The signal of the anomeric proton appeared at 5.30 ppm as a triplet (J = 1.8 Hz) which collapsed to a sharp singlet on D_2O addition. This indicated the presence of an imino group bonded with $C_{1'}$ and absence of interaction between $H_{1'}$ and $H_{2'}$. The reason for the appearance of the anomeric proton signal as a triplet, not as a doublet, is uncertain at present.[17] In addition, no signal corresponding to an isolated heteroaromatic proton was observed. Thus, in spite of the ambiguous resonance of $H_{1'}$, there is no obvious reason to support the alternative structure, **9′**.[18,19]

The azide reactions were then applied to a few cytidine analogues. 2′,3′-*O*-Isopropylidene-5-bromocytidine (**10**)[20] was treated with methanesulfonyl chloride to give a good yield of 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-5-bromocytidine (**11**) as crystals. A TLC controlled reaction of **11** with sodium azide revealed two main products at the stage of disappearance of the starting material (see Experimental Section). In this case, extensive resinification was inevitable but preparative TLC permitted isolation of these products, the faster moving of which was a foam (14%) presenting an azide absorption at 2120 cm^{-1} (KBr) and uv absorption at 284 nm. These spectral data immediately permitted the conclusion that its structure was 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromocytidine (**12**), also supported by the following description. The slower moving crystalline product (8%) was 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**) on the basis of analysis and spectral data.[21] For comparison, the uv spectra of **3a** and **13**



are represented in Figure 1, which also includes the CD spectrum of **3a**.[22] Compound **12** was formed in much higher yield (73%) in neutral medium[23] using ammonium azide generated in situ. Thermal conversion of **12** into **13** was, however, accompanied by resinification, giving merely 15% of **13**.

The formation of 9,5′-cyclized nucleosides **3a,b** and **13** from **2a–c** and **11** was unexpected and posed the question whether the actual intermediates were exclusively 5′-azido-5′-deoxy compounds like **6** and **12** or not. Although **13** was isolated as a by-product in the reaction of **11**, this did not preclude 8-azaxanthine or 8-azaisoguanine nucleosides with a leaving group of C-5′ as intermediates, in which ionized 9-NH could easily substitute at the 5′ methylene (the same chance would be open also for 2-keto oxygen in such a case). In a separate experiment, we synthesized 5′-*O*-trityl-2′,3′-*O*-isopropylidene-5-bromouridine (**14**) and submitted

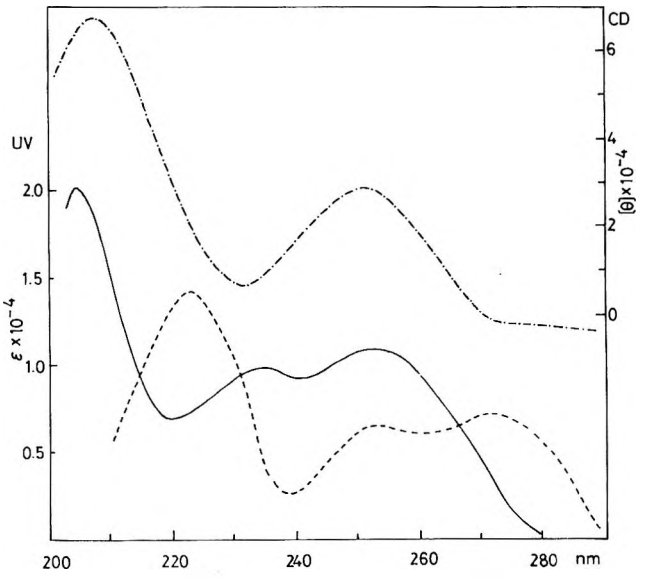
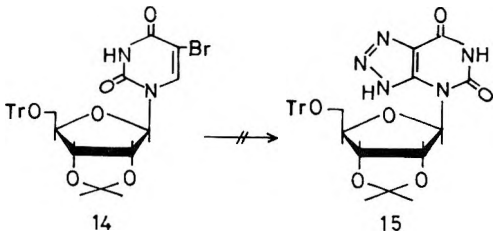


Figure 1. Uv [—, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (**3a**); - - -, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**)] and CD spectra (**3a**) in methanol.

it to a similar azide reaction, but starting material only was recovered after 50-h reaction at 110 °C with 5.5-fold excess sodium azide. This suggests that 5-bromopyrimidine bases



are unexpectedly inert toward external azide ion and that 5′-azido-5′-deoxy compounds are the only intermediates in our reactions. The persistence of **12** and extensive degradation in the case of the cytidine analogue (**11**) are in contrast to the behavior of uracil analogues (**2a–c**). This would imply that the 6 position in 5-bromocytidine analogues is far less electrophilic and hence complex reactions initiated by thermal decomposition of the 5′-azide group preceded its nucleophilic attack on the base moiety.[24]

In conclusion, this work presents the possibility of a one-step synthesis of other types of 6,5′-cyclized nucleosides using proper nucleophiles.

Experimental Section

All the melting points are uncorrected. The ultraviolet spectra were measured on a Jasco Model ORD/UV spectrophotometer. The nuclear magnetic resonance spectra were determined using a JNM C-60 HL spectrometer and tetramethylsilane as a internal standard, while the 100-MHz spectra were recorded with a Varian HA-100 spectrometer.[11] The circular dichroism spectrum was recorded with a Jasco Model J-20 recording spectropolarimeter in the laboratory of Professor H. Ogura, Kitazato University, Tokyo, for which we are grateful. Elemental analyses were carried out by Miss Y. Kawai using a Perkin-Elmer 240 elemental analyzer in this laboratory. Wakogel B-5 silica gel and Mallinkrodt silicic acid (100 mesh) were used for thin layer and column chromatography, respectively.

2′,3′-*O*-Anisylidene-5-bromouridine (1b). To a mixture of 5-bromouridine (2.68 g), anisaldehyde (1.5 ml), and ethyl orthoformate (3 ml) in DMF (8.3 ml) was added saturated hydrogen chloride solution in dioxane (2.5 ml). After standing overnight, the mixture was neutralized with solid sodium bicarbonate and the inorganic material was filtered off. The filtrate was evaporated in vacuo to a gum, which was partitioned between ethyl acetate (200

ml) and water (50 ml). The separated ethyl acetate solution was dried over sodium sulfate and evaporated to a paste, which was triturated with a small volume of ether. The ethereal solution was decanted off, and the residue was digested with a small amount of methanol to effect crystallization. Repeated crystallization from a mixture of ethanol and acetone gave colorless needles, mp 224–226 °C (2.16 g, 59%).

Anal. Calcd for $C_{17}H_{17}N_2O_7Br$: C, 46.27; H, 3.88; N, 6.35. Found: C, 46.34; H, 3.87; N, 6.29.

5′-*O*-Benzoyl-2′,3′-*O*-isopropylidene-5-bromouridine (2a). Benzoyl chloride (0.5 ml, 4.6 mmol) was slowly added to a stirred, ice-cold solution of 2′,3′-*O*-isopropylidene-5-bromouridine (**1a**, 1.39 g, 3.83 mmol) in pyridine (8 ml). After stirring under ice cooling for 1 h, the mixture was left at room temperature for several hours and evaporated in vacuo to a syrup. This was dissolved in methanol (20 ml) and poured into ice–water (200 ml) under vigorous stirring. The precipitate was collected by suction, dried on a porous plate, and recrystallized from methanol to give colorless needles (1.50 g, 84%): mp 206–208 °C; λ_{max} (MeOH) 225 nm (ϵ 13 500) and 274 (8300).

Anal. Calcd for $C_{19}H_{19}N_2O_7Br$: C, 48.88; H, 4.10; N, 5.99. Found: C, 49.07; H, 4.22; N, 5.99.

2′,3′-*O*-Isopropylidene-5′-*O*-tosyl-5-bromouridine (2b). Tosyl chloride (0.3 g, 1.56 mmol) was added to an ice-cold stirred solution of **1a** (0.5 g, 1.3 mmol) in pyridine (3 ml) and the mixture was left at room temperature overnight. After addition of further tosyl chloride (0.1 g), the mixture was stirred at room temperature for 3 h, treated with a small amount of water, and then evaporated in vacuo. The residue was taken into chloroform (30 ml), washed with water (10 ml), dried over sodium sulfate, and evaporated. Crystallization from benzene gave **2b** as prisms containing a molecule of benzene: mp 125–127 °C; yield 80–85%; λ_{max} (MeOH) 220 nm (ϵ 18 600) and 270 (10 200).

Anal. Calcd for $C_{19}H_{21}N_2O_8SBr \cdot C_6H_6$: C, 50.42; H, 4.53; N, 4.71. Found: C, 50.70; H, 4.67; N, 4.95.

2′,3′-*O*-Anisylidene-5′-*O*-benzoyl-5-bromouridine (2c). To a stirred ice-cold solution of **1b** (1.05 g, 2.4 mmol) in pyridine (6 ml) was added benzoyl chloride (0.32 ml, 2.88 mmol), and the mixture was stirred at room temperature for several hours. After the reaction was quenched with a small amount of water, the mixture was evaporated, redissolved in acetone (10 ml), and precipitated into ice–water (150 ml). The separated solid was air dried and recrystallized from a mixture of methanol and ethyl acetate to give 1.08 g (83%) of **2c** as needles: mp 221–223 °C; λ_{max} (MeOH) 224 nm (ϵ 34 800) and 272 (13 500).

Anal. Calcd for $C_{24}H_{21}N_2O_8Br$: C, 52.86; H, 3.88; N, 5.14. Found: C, 52.77; H, 3.97; N, 5.14.

9,5′-Cyclo-3-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (3a). Method A. A mixture of **2a** (1.88 g, 4.0 mmol) and sodium azide (480 mg, 7.4 mmol) in DMF (16 ml) was stirred at 110 °C for 30 h. During the reaction, an aliquot was taken every 2 or 3 h, thoroughly evaporated, and examined by TLC using solvent systems ethyl acetate–chloroform (3:1 v/v), 20% ethanol in benzene, 10% methanol in chloroform, etc., to show only one product with the starting material. After further addition of sodium azide (240 mg, 3.7 mmol), the reaction was continued for an additional 10 h, until the starting material disappeared. The mixture was cooled, the insoluble material filtered off, and the filtrate evaporated in vacuo to a paste, which was extracted with ethyl acetate (3 × 50 ml) in the presence of water (50 ml). The ethyl acetate solution was back-washed with water (10 ml), dried over sodium sulfate, and evaporated to give a crystalline residue. Recrystallization from a mixture of methanol and ethyl acetate gave 844 mg (70%) of **3a** as colorless plates: mp above 300°; λ_{max} (MeOH) 235 nm (ϵ 9800) and 255 (10 500); MS *m/e* 307 (M^+), 292 ($M^+ - CH_3$); NMR (Me_2SO-d_6 + D_2O) δ 1.27 (3 H, s, Me), 1.48 (3 H, s, Me), 4.60 (1 H, dd, J_{gem} = 12, $J_{4',5'b}$ = 4.5 Hz, $H_{5'b}$), 4.84 (1 H, d, $J_{4',5'b}$ = 4.5 Hz, $H_{4'}$, partially overlapped on the signals of $H_{2'}$ and $H_{3'}$), 4.88 (2 H, br s, $H_{2'}$ and $H_{3'}$), 5.16 (1 H, d, J_{gem} = 12 Hz, $H_{5'a}$), and 6.32 (1 H, s, $H_{1'}$).

Anal. Calcd for $C_{12}H_{13}N_5O_5$: C, 46.90; H, 4.26; N, 22.80. Found: C, 47.09; H, 4.32; N, 22.53.

Method B. A mixture of **2b** (521 mg, 0.88 mmol) and sodium azide (57 mg, 0.88 mmol) in DMF (5 ml) was stirred at 110 °C for 5 h. After another addition of sodium azide (57 mg, 0.88 mmol), heating was continued for a further 10 h, during which most of the starting material was consumed. The mixture was evaporated to a gum and worked up as in procedure A to give 100 mg (37%) of **3a**, identified with the product in procedure A by ir and uv spectra.

9,5′-Cyclo-3-(2′,3′-*O*-anisylidene-β-D-ribofuranosyl)-8-azaxanthine (3b). A mixture of **2c** (992 mg, 1.87 mmol) and sodium azide (240 mg, 3.7 mmol) in DMF (8 ml) was stirred at 110 °C for 20 h. Additional sodium azide (120 mg, 1.85 mmol) was added and the mixture was held under the same conditions for another 10 h. The reaction was worked up essentially as for compound 3a. Crystallization from acetonitrile gave **3b** as fine needles (650 mg, 65%): mp above 280°; λ_{max} (MeOH) 225 nm (ϵ 24 600) and 255 (13 300).

Anal. Calcd for $C_{17}H_{15}N_5O_6$: C, 52.99; H, 3.90; N, 18.18. Found: C, 53.01; H, 3.99; N, 18.11.

9,5′-Cyclo-3-β-D-ribofuranosyl-8-azaxanthine (4). A mixture of **3a** (0.1 g) and IRA-120 (H^+ form, 8 ml) in 90% methanol (40 ml) was heated to reflux for 15 h. TLC using silica gel and 20% ethanol in benzene showed the presence of a single product and no starting material. The resin was filtered and washed with 90% methanol (50 ml) and the total was evaporated to give a solid residue. Recrystallization from methanol gave 70 mg (72%) of needles (**4**), which gradually decomposed between 270 and 280 °C.

Anal. Calcd for $C_9H_9N_5O_5 \cdot CH_3OH$: C, 40.14; H, 4.38; N, 23.14. Found: C, 39.97; H, 4.15; N, 23.14.

This methanolate, on crystallization from hot water, gave the solvent-free product as massive columns which also began to decompose at around 270 °C and did not melt at below 300 °C: λ_{max} (MeOH) 240 nm (ϵ 8050) and 257 (10 800); MS *m/e* 267 (M^+); NMR (Me_2SO-d_6 + D_2O) δ 4.22 (1 H, dd, J_{gem} = 12, $J_{4',5'b}$ = 4.5 Hz, $H_{5'b}$), 4.22 (1 H, d, $J_{4',5'b}$ = 4.5 Hz, $H_{4'}$, partially overlapped on the signal of $H_{5'b}$), 4.68 (1 H, quintet, J = 3.6 Hz, $H_{2'}$ or $H_{3'}$), 4.91 (1 H, d-like quartet, J = 3.6 Hz, $H_{3'}$ or $H_{2'}$), 5.06 (1 H, d, J_{gem} = 12 Hz, $H_{5'a}$), and 6.09 (1 H, s, $H_{1'}$).

Anal. Calcd for $C_9H_9N_5O_5$: C, 40.45; H, 3.37; N, 26.21. Found: C, 40.71; H, 3.61; N, 26.40.

Compound **4** can be more conveniently prepared by heating **3a** (50 mg) in 1 N hydrochloric acid (6 ml) at 95–100 °C for 5–6 h. **3b** was analogously hydrolyzed to **4**.

Reconversion of 4 into 3a. A mixture of the methanolate of **4** (20 mg, 0.067 mmol), acetone (0.2 ml), ethyl orthoformate (0.05 ml), DMF (0.4 ml), and saturated hydrogen chloride solution in dioxane (3 drops) was left at room temperature for 18 h, neutralized with solid sodium bicarbonate, and filtered by suction after adding DMF (2 ml). The filtrate was evaporated in vacuo and the residue partitioned between ethyl acetate (30 ml) and water (10 ml). The separated ethyl acetate layer was worked up as usual to give 13 mg of homogeneous crystals, which was identified with **3a** by ir and uv spectra.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (6). *N*-Bromoacetamide (320 mg, 2.3 mmol) was added to a solution of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**5**. 642 mg, 2.1 mmol) in anhydrous tetrahydrofuran (9 ml) and the mixture was stirred at room temperature for 3 h. TLC using chloroform–ethyl acetate (1:1 v/v) as developer indicated quantitative conversion of **5** into a faster moving substance. The solvent was evaporated off below 40 °C and the residue was partitioned between ethyl acetate (15 ml) and ice–water (5 ml). The separated organic phase was dried over sodium sulfate and evaporated to a gum, which crystallized from ethanol to afford 640 mg (79%) of **6** as granules of mp 165–167°: λ_{max} (MeOH) 272 nm (ϵ 10 200); ir (KBr) ν_{N_3} 2100 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}BrN_5O_5$: C, 37.11; H, 3.61; N, 18.04. Found: C, 37.24; H, 3.64; N, 17.88.

Thermal Conversion of 6 into 3a. A solution of **6** (300 mg, 0.775 mmol) in DMF (20 ml) was heated at 110–120 °C for 20 h. TLC at this stage revealed only one product corresponding to **3a** and no starting material. The solvent was evaporated off in vacuo, and the residue was thoroughly digested with ice–water (3 ml). The solid was collected by suction, dried on a porous plate, and crystallized from methanol to give 210 mg (70%) of **3a**, identical with the above authentic sample in terms of ir and uv spectra.

***N*¹,5′-Anhydro-*N*⁵-(2′-3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-carboxyhydrazino-5-amino-*v*-triazole (9). 3a** (138 mg, 0.45 mmol) was dissolved in 85% hydrazine (2.3 ml) by shaking and the solution was left at room temperature. After 30 min, crystals began to deposit. TLC after 2 h reaction indicated no starting material. After a total of 3 h, the mixture was evaporated in vacuo below room temperature and the residue repeatedly coevaporated with ethanol to remove residual water and hydrazine. Crystallization of the residual solid from methanol gave 78 mg (59%) of **9** as colorless needles: mp 233–235 °C; λ_{max} (MeOH) 238 nm (ϵ 14 000) and 259 (10 000, sh); MS *m/e* 296 (M^+), 239 ($M^+ - CH_3COCH_3 + H^+$); NMR (Me_2SO-d_6) δ 1.19 (3 H, s, Me), 1.39 (3 H, s, Me), 3.00–3.70 (~3 H, br s, NH_2 of the hydrazino group and 5-NH), 4.12 (1 H, dd, J_{gem} = 14.0, $J_{4',5'a}$ = 2.3 Hz, $H_{5'a}$), 4.28 (1 H, d, $J_{2',3'}$ = 6.0

Hz, $H_{2'}$ or $H_{3'}$), 4.54 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$ or $H_{2'}$), 4.55 (1 H, t, $J_{4',5'b}$ = 2.3 Hz, $H_{4'}$), 4.94 (1 H, dd, J_{gem} = 14.0, $J_{4',5'b}$ = 2.3 Hz, $H_{5'b}$), 5.30 (1 H, t, J = 1.8 Hz, $H_{1'}$, collapsed to a singlet on D_2O addition), 7.50 (1 H, d, J = 4.0 Hz, O=CNH–, D_2O exchangeable).

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.79; H, 5.42; N, 28.39.

2',3'-*O*-Isopropylidene-5'-*O*-methanesulfonyl-5-bromocytidine (11). Methanesulfonyl chloride (0.3 ml, 3.87 mmol) was gradually added to a stirred solution of **10** (1.16 g, 3.2 mmol) in pyridine (8 ml) which had been precooled up to −20 °C. After standing at this temperature overnight, the mixture was left at room temperature for 1 h and treated with methanol (1 ml) for another 1 h. The solvent was evaporated in vacuo below room temperature and the residue was partitioned between ethyl acetate (90 ml) and ice–water (30 ml). The separated organic phase was dried over sodium sulfate and evaporated to a paste, which crystallized on standing with a small amount of ethanol. Recrystallization from ethanol at room temperature gave 990 mg (70%) of needles (**11**), mp 202–204 °C dec, λ_{max} (MeOH) 284 nm (ϵ 6800).

Anal. Calcd for $C_{13}H_{18}N_3O_7SBr$: C, 35.46; H, 4.12; N, 9.54. Found: C, 35.73; H, 4.31; N, 9.38.

Reaction of Sodium Azide with 2',3'-*O*-Isopropylidene-5'-*O*-methanesulfonyl-5-bromocytidine (11). A mixture of **11** (440 mg, 1 mmol) and sodium azide (120 mg, 1.85 mmol) in DMF (5 ml) was stirred at 110 °C. After 24 h, further sodium azide (65 mg, 1 mmol) was added and heating continued for an additional 9 h. During the reaction, an aliquot was withdrawn every 2 or 3 h and examined by TLC using the solvent systems, 10% methanol in chloroform and/or 30% ethanol in benzene, to show the formations of two main products with slight amounts of by-products. A considerable degree of resinification was observed. The dark mixture was filtered to remove inorganic materials and the filtrate was evaporated in vacuo. The residue was triturated with ice–water (10 ml) and the solid precipitate was collected. The aqueous filtrate was extracted with ethyl acetate (60 ml) and the extract was combined with the above obtained precipitate. The solution of the product was then dried over sodium sulfate and evaporated to a gum, which was then charged on a silica gel plate (20 × 20 cm, 2 mm thick) and developed twice using 10% methanol in chloroform. Elution of the faster moving main band with acetone and ethanol gave 70 mg (14%) of 5'-azido-5'-deoxy-2',3'-*O*-isopropylidene-5-bromocytidine (**12**) as a homogeneous foam, which resisted crystallization, ir (Kbr) ν_{N_3} 2120 cm^{-1}, λ_{max} (MeOH) 284 nm (ϵ ~7000).

On the other hand, the slower moving band gave 50 mg (8%) of 9,5'-cyclo-3-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**) as powderlike crystals after recrystallization from ethanol: mp 197–199 °C; λ_{max} (MeOH) 223 nm (ϵ 14 200), 253 (6400), and 271 (7000); NMR ($CDCl_3$) δ 1.30 (3 H, s, Me), 1.52 (3 H, s, Me), 4.40–5.40 (5 H, br s, $H_{2'}$, $H_{3'}$, $H_{4'}$, and 5'-CH_2), 6.70 (1 H, s, $H_{1'}$), 7.35 (1 H, br s, NH, D_2O exchangeable), and 9.20 (1 H, br s, NH, D_2O exchangeable).

Alternative Synthesis of 5'-Azido-5'-deoxy-2'-3'-*O*-isopropylidene-5-bromouridine (12) from 11 and Ammonium Azide. A mixture of **11** (765 mg, 1.74 mmol), sodium azide (210 mg, 3.23 mmol), and ammonium chloride (175 mg, 3.27 mmol) in DMF (8 ml) was stirred at 90 °C for 10 h. After cooling, inorganic materials were filtered off and the filtrate was evaporated in vacuo. The red-brown residue was triturated with ice–water (10 ml) to give a precipitate, which was filtered by suction. The filtrate was extracted with ethyl acetate (100 ml) and the separated organic phase was combined with the above obtained precipitate. The solution was dried and evaporated to a foam, which was chromatographed on a silica gel plate (20 × 20 cm, 2 mm thick) using 10% methanol in chloroform (twice developed). The main band gave 490 mg (73%) of **12** as a homogeneous foam, identified with the above obtained product by ir and uv spectra. A slight amount of **13** was also detected by TLC but was neglected.

Thermal Conversion of 12 into 13. The above obtained **12** (490 mg, 1.26 mmol) in DMF (10 ml) was heated at 120 °C for 12 h. TLC showed one main, movable product corresponding to **13** and no starting material. The mixture was evaporated to a dark residue, which was dissolved in methanol (20 ml), adjusted to pH 7–8 with concentrated ammonium hydroxide–methanol (1:3 v/v), and again evaporated to a tar. This was extracted with hot acetone (4 × 30 ml) and the combined extract was submitted to preparative TLC (20 × 20 cm, 2 mm thick; $CHCl_3$–MeOH, 9:1). Elution of the main band with acetone gave 60 mg (15%) of practically pure powder, which was fully identified with an authentic specimen of **13**.

Registry No.—**1a,** 54503-61-6; **1b,** 57901-58-3; **2a,** 57901-59-4; **2b,** 57901-61-8; **2c,** 57901-62-9; **3a,** 57901-63-0; **3b,** 57901-64-1; **4,** 57901-65-2; **4** CH_3OH, 57968-00-0; **5,** 15083-05-3; **6,** 57901-66-3; **9,** 57901-67-4; **10,** 57901-68-5; **11,** 57901-69-6; **12,** 57901-70-9; **13,** 57901-71-0; 5-bromouridine, 957-75-5; anisaldehyde, 123-11-5; benzoyl chloride, 98-88-4; sodium azide, 26628-22-8; *N*-bromoacetamide, 79-15-2; methanesulfonyl chloride, 124-63-0.

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(15) N. S. Bhacca and D. H. Williams, Ed., "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 50.
(16) Measurement in Me_2SO-d_6 without D_2O revealed two hydroxyl proton signals at 5.31 (J = ~6.2 Hz) and 5.63 ppm (J = ~3.9 Hz) and also a signal for a lactam NH at 11.35 ppm (br s) besides rather more complicated signals for the other furanose protons.
(17) A close inspection of the NMR spectrum of **9** in Me_2SO-d_6 without D_2O revealed, besides the broad resonance at 3.0–3.7 ppm, a very broad, shallow signal envelope (~0.5 H) at 8.8–9.5 ppm, which was D_2O exchangeable. This might suggest possibilities for a variety of partial hydrogen bondings between the 4-carboxyhydrazino and 5-imino groups. Actually, it is possible to write down variously six-membered rings hydrogen bonded between the 5-NH and the carbonyl oxygen or hydrazino NH with or without concomitant five-membered hydrogen bonding within the carboxyhydrazino group. However, no conclusion can be drawn regarding the well-resolved, sharp triplet.
(18) A short treatment of **9** with acetone at room temperature gave a faster moving (on a silica gel plate) syrup (probably acetone hydrazone), whose complete purification was, however, unsuccessful.
(19) It is interesting to note that hydrazine attacked C-6 of the 8-azaxanthine ring. This observation is parallel with the hydrazinolysis of thymidylic acid, which occurs at C-4 of the pyrimidine base: A. Temperli, H. Türler, P. Rüst, A. Danon, and E. Chargaff, *Biochim. Biophys. Acta*, **91**, 462 (1964).
(20) A good yield synthesis of this compound was learned from Dr. T. Ueda through private communication, for which we are grateful.
(21) The NMR spectrum measured at 60 MHz using a very limited amount of **13** failed to give clear-cut resonances for most of the sugar protons. Our tentative assignment of the structure with a 6-imino group is based on the separate apparitions of the two NH signals.
(22) The positive Cotton effect at around 250 nm is reminiscent of the known positive Cotton effects of purine 8-cyclonucleosides: M. Ikehara, *Acc. Chem. Res.*, **2**, 47 (1969).
(23) According to our experiences, a reaction mixture containing ammonium azide usually indicates a practically neutral pH when equimolar ammonium chloride and sodium azide are used. Moreover, ammonium azide seems to be more soluble in DMF than sodium azide.
(24) A trial experiment has shown that pyrolysis of **7** in DMF smoothly proceeds at 115–120 °C to give a highly insoluble polymeric compound, the structure of which is unknown at present.

Molecular Design by Cycloaddition Reactions. XXV.[1] High Peri- and Regiospecificity of Phencyclone

Tadashi Sasaki,* Ken Kanematsu, and Kinji Iizuka

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464, Japan

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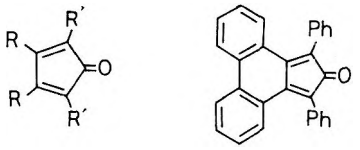
The cycloaddition reactions of phencyclone with electron-rich and -deficient olefins and seven-membered ring unsaturated polyenes are extensively investigated. The structural elucidations of these adducts were accomplished by spectral inspections. The high peri- and regiospecificity of phencyclone was observed. Some formation mechanisms for the adducts are discussed by the frontier orbital model.

It is well known that cyclopentadienone and its analogues (**1**) are reactive and versatile diene components in the Diels–Alder reactions.[2,3] We have described the cycloaddition reactions of cycloheptatriene with 2-pyrone derivatives to give novel bridged cage adducts.[4]

As a continuation of our previous work,[1] we now describe the cycloaddition reactions of phencyclone (**2**) with seven-membered ring unsaturated compounds and olefinic dienophiles; phencyclone (**2**) is known as a more reactive and stable diene compound than other cyclopentadienone derivatives.[5] However, no systematic study has been reported on its cycloaddition reactions.

Chart I



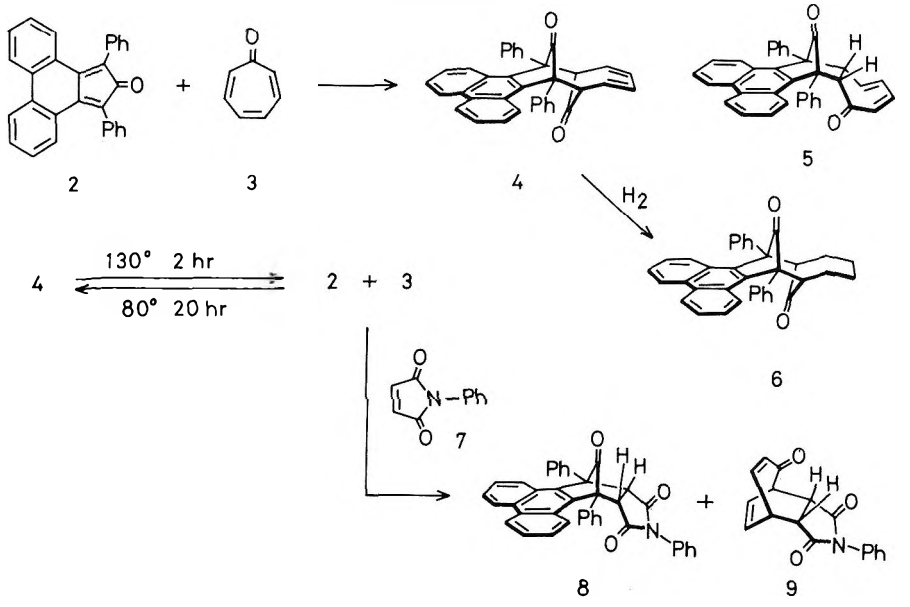
1 2

Results

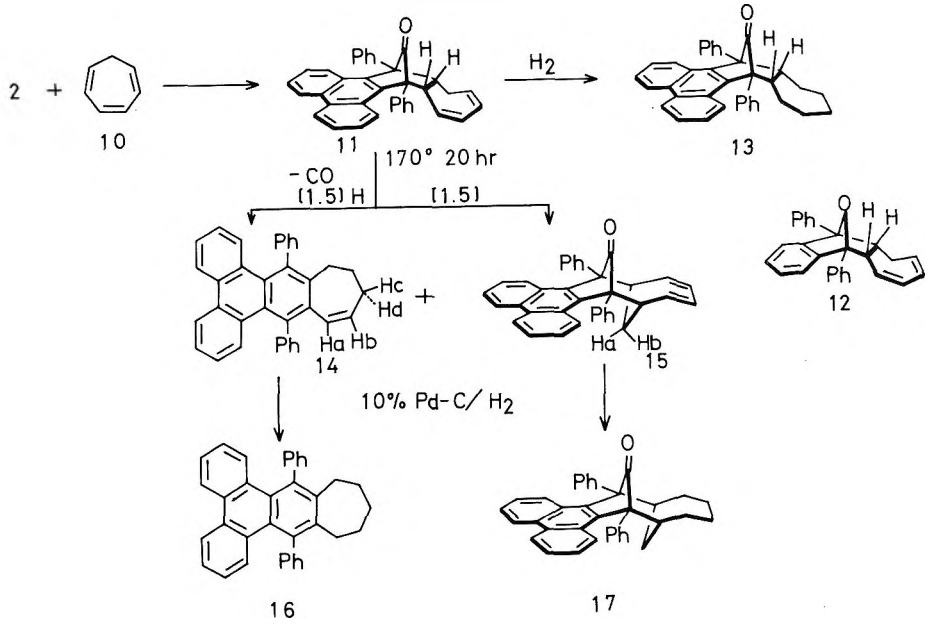
Cycloaddition Reaction of Phencyclone with Seven-Membered Ring Polyenes. With Tropone. Reaction of phencyclone (**2**) with two equimolar amounts of tropone (**3**) in benzene at 80 °C for 20 h gave a 1:1 adduct **4** in 70% yield. The ir spectrum of **4** showed two characteristic bands at 1780 and 1725 cm^{-1} due to strained ring carbonyl and nonconjugated carbonyl groups, respectively. Furthermore, the NMR spectrum of **4** showed four vinyl protons as a multiplet centered at δ 6.17 and two bridgehead protons as a doublet at δ 4.60 suggesting a highly symmetrical structure,[6] and therefore, the structure of [4 + 2] adduct **5** could be ruled out. Catalytic hydrogenation of **4** over palladium on charcoal gave a tetrahydro compound **6** in quantitative yield, which showed two carbonyl bands at 1778 and 1718 cm^{-1} similar to that of compound **4** by the ir. From these data, the adduct **4** was suggested as a structure of the [6 + 4] adduct. Furthermore, the configuration of the [6 + 4] adduct could be determined to be exo, since the olefinic protons in the endo isomer might be shielded by the anisotropy of the phenanthrene moiety in comparison with the corresponding position in structure **54** (see Table VI). Pyrolysis of the adduct **4** in chlorobenzene at 130 °C for 2 h afforded the cycloreversion products, **2** and **3**, which was further confirmed by the formation of **8** and **9**[7] in the presence of *N*-phenylmaleimide (**7**) in the pyrolysis of **4** (Scheme I).

With Cycloheptatriene. A solution of **2** and an excess amount of cycloheptatriene (**10**) was heated in benzene at 80 °C for 16 h in a sealed tube under argon, and chromatographed on silica gel to give a 1:1 adduct **11** in 57% yield. The adduct **11** showed a characteristic band at 1790 cm^{-1} due to a strained carbonyl band by the ir, and methylene proton signals at δ 1.4–2.0 (m, 1 H) and 2.35–2.80 (m, 1 H), methine protons at δ 4.15 (m, 2 H), and olefinic protons at δ 5.2–6.3 (m, 4 H) by the NMR. The NMR spectral pattern of the cycloheptadiene moiety of **11** is very similar to that of an endo [4 + 2] adduct **12**[8] in the thermal cycloaddition of 1,3-diphenylisobenzofuran to cycloheptatriene (**10**). Catalytic hydrogenation of **11** over palladium on charcoal gave a tetrahydro compound **13** in quantitative yield. From

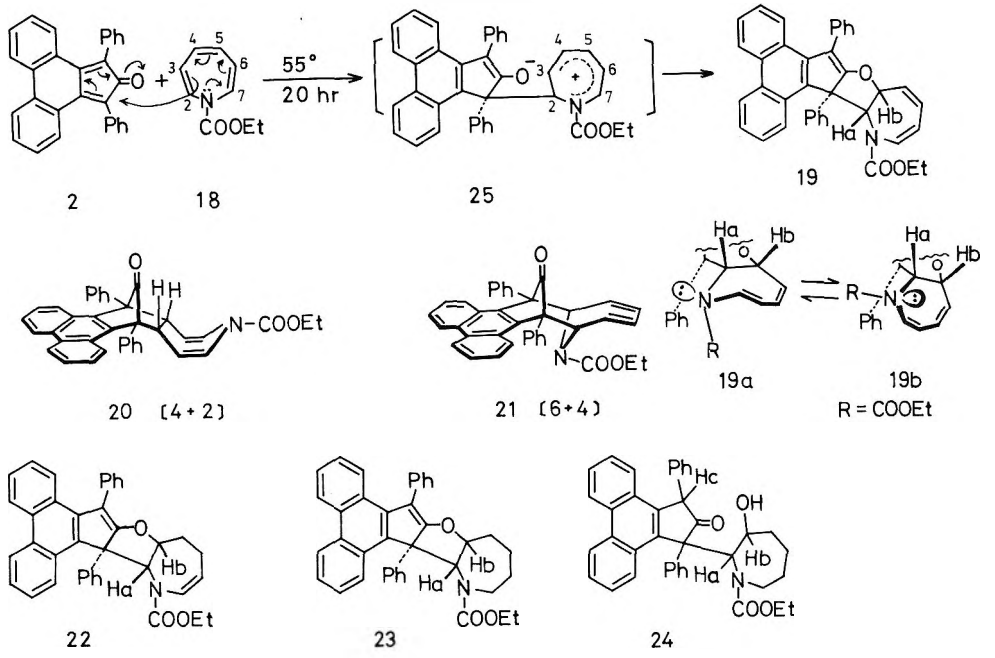
Scheme I



Scheme II



Scheme III



these data, the adduct **11** was assigned as a structure of the endo [4 + 2] compound. When the adduct **11** was heated in chlorobenzene at 170 °C for 20 h, the decarbonylated product **14** (34%) and the rearranged product **15** (47%) were obtained. The ir spectrum of **14** showed no carbonyl band, and the NMR spectrum displayed two benzylic protons at δ 2.68 as multiplets, four methylene protons at δ 2.20 as multiplets, and two olefinic protons at δ 6.0 (dd, J = 11.5 and 5.5 Hz) and 6.57 (d, J = 11.5 Hz). An appearance of a double doublet of one olefinic proton indicated that the dihedral angles between H_b and H_d are approximately 90° by a stereomodel inspection and, thus, only the protons in H_b and H_a, and H_b and H_c should be coupled. Catalytic hydrogenation of **14** over palladium on charcoal gave a dihydro compound **16** in quantitative yield. On the other hand, the ir spectrum of **15** showed a characteristic carbonyl band at 1768 cm^{-1} suggesting the presence of a bridged carbonyl group. The NMR spectrum of **15** showed two bridged methylene protons at δ 1.58 (m), two bridgehead protons at δ 4.05 (m), and four olefinic protons at δ 5.8–6.75 (m) suggesting a symmetrical structure of exo [6 + 4] adduct;[8] the lack of upfield shift of the methylene bridge protons could be explained by examination of a stereomodel showing that the protons are not closed to the phenanthrene moiety in comparison with that of compounds **33** and **35** (see later). By contrast, the methylene bridge protons in the endo isomer will be shifted strongly by the carbonyl anisotropy.[8] Similar catalytic hydrogenation of **15** gave a tetrahydro compound **17** in quantitative yield.

From the above data, the structures of **14** and **15** were assigned as depicted in Scheme II.

Thus, the formation of compound **14** might proceed initially producing a decarbonylated intermediate followed by successive 1,5-hydrogen shift, while the formation of compound **15** might proceed stereospecifically by the thermally allowed 1,5-sigmatropic shift, and also could arise from the endo [4 + 2] adduct **11**.

The NMR spectra of compounds **4**, **6**, **11**, and **13**–**17** are

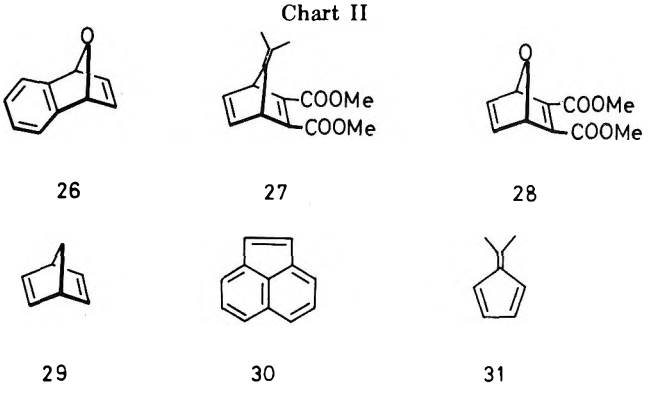
summarized in Table I (see paragraph at end of paper regarding supplementary material).

With *N*-Carbethoxyazepine. A solution of phencyclone (**2**) and equimolar amounts of *N*-carbethoxyazepine (**18**) in benzene was heated at 55 °C for 20 h (or at 100 °C for 3 h) under argon to give a 1:1 adduct **19** in quantitative yield. The adduct **19** exhibited ir bands at 1700 (urethane carbonyl) and 1640 cm^{-1} (olefinic band), and no absorption due to strained ring carbonyl.

The mass spectrum showed a characteristic molecular ion peak at *m/e* 547 and intense peaks at *m/e* 165, 92, and 65 due to characteristic fragmentation of *N*-carbethoxyazepine.

The NMR spectrum was complexed and not compatible with symmetrical structures such as [4 + 2] adduct **20** and [6 + 4] adduct **21**; it displayed methyl protons of the carbethoxy group as two kind of triplets centered at δ 0.85, and also signals at δ 3.3–4.0 (m, 3 H, CO_2CH_2– and H_a), 4.7–5.2 (m, 1 H, H_b), 5.3–5.85 (m, 2 H, olefinic H), and 6.4–8.1 (complex m, 20 H, aromatic and two olefinic H). Catalytic hydrogenation of the adduct **19** over 10% palladium on charcoal gave a mixture of dihydro (**22**) and tetrahydro compounds (**23**) in a ratio of 5:1. Similar catalytic hydrogenation of **19** over Adams catalyst in the presence of small amounts of acetic acid gave only tetrahydro compound **23** in quantitative yield. The NMR spectrum of **22** exhibited signals at δ 5.62 (m, 1 H) and 6.5–6.8 (m, 1 H) due to enamino olefins, while the NMR spectrum of **23** exhibited no olefinic proton signals. The NMR spectra of compounds **19** and **23** displayed the methyl proton signals of the carbethoxy group as a triplet at 120 °C (each δ 0.79, J = 7.5 Hz), but as a multiplet at 60 °C in pyridine-d_5 solution, respectively. This suggests that compounds **19, 22,** and **23** exist in an equilibrium of two kinds of conformational isomers **19a** and **19b** at room temperature as depicted in Scheme III. Compounds **19** and **23** were inert for reduction with sodium borohydride or for alkaline hydrolysis with methanolic potassium hydroxide. However, hydrolysis of compound **23** with hydrochloric acid in methanol gave compound **24**; its ir spectrum showed characteristic bands at 1745 (five-membered ring carbonyl) and 1680 cm^{-1} (urethane carbonyl). Thus, the formation of **24** might proceed by cleavage of a vinyl ether–carbon bond in compound **23.** Thus, compound **19** might be derived from initial attack at the C-2 position of *N*-carbethoxyazepine (**18**) followed by ring closure of an intermediate dipolar ion (**25**) to give a formal [6 + 2] adduct as shown in Scheme III. The NMR spectra of these compounds are summarized in Table II.

Chart II



26 27 28 29 30 31

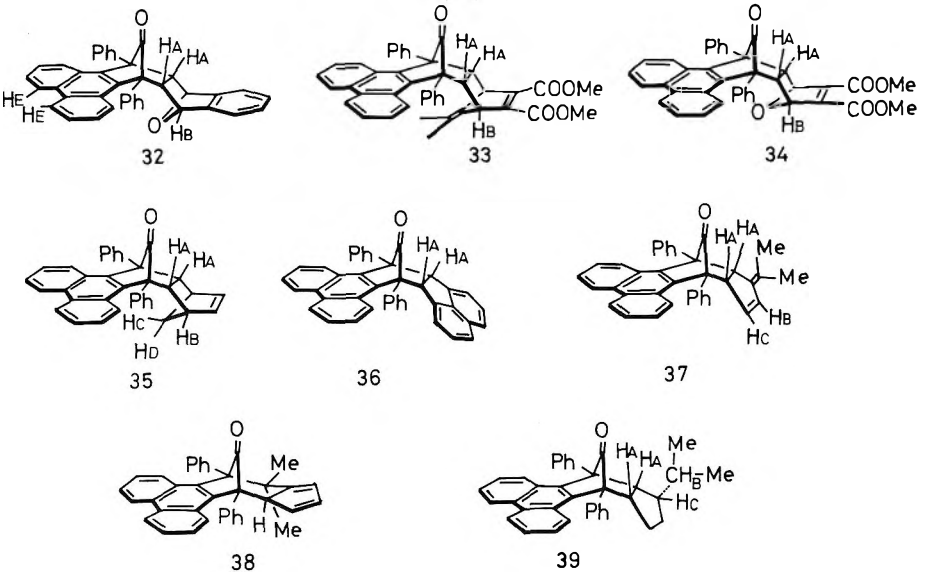
Cycloaddition Reactions of Phencyclone with Olefinic Dienophiles. In order to further investigate the reactivity of phencyclone (**2**), we attempted the thermal cycloaddition reactions of phencyclone (**2**) with a variety of electron-rich (**26–31**) and electron-deficient olefins (**7, 45–51**).

With Electron-Rich Olefins. Phencyclone (**2**) and equimolar amounts or an excess of the olefins (**26–31**) react to give 1:1 adducts (**32–37**) in high yields. The ir spectra of these adducts showed common characteristic bands at 1780–1800 cm^{-1} due to a strained ring carbonyl group. Interestingly, in the NMR spectra compounds **33** and **35** exhibited a very strong anisotropic effect of isopropylidene methyl signals as a singlet (δ −0.17), and bridged methylene proton signals as an AB quartet at δ 0.43 and −0.43 due to the phenanthrene ring current effect, suggesting strongly the structures of endo, exo [4 + 2] adducts. The NMR spectrum of **37** exhibited two olefinic proton signals as an AB quartet centered at δ 5.60 and 5.76, suggesting endo [4 + 2] adduct but no [6 + 4] adduct, since the [6 + 4] adduct **38** should display three olefinic proton signals. Catalytic hydrogenation of **37** over palladium on charcoal gave a tetrahydro compound **39** in quantitative yield. Thus, structural proofs of these adducts, **32–37,** were based on elemental analyses and spectroscopic data.

The reaction conditions for these addition reactions are summarized in Table III.

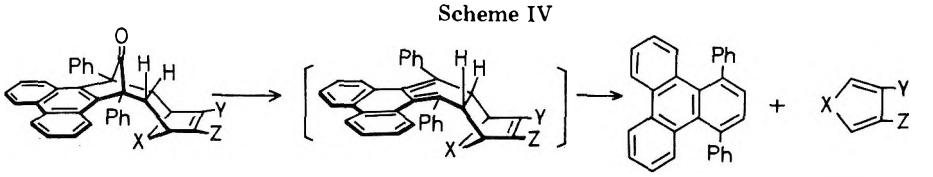
The NMR spectral data for these adducts are summarized in Table IV.

Chart III



32 33 34 35 36 37 38 39

Scheme IV



32 X = O, YZ = 
33 X = C=CMe$_2$, Y=Z=COOMe
34 X = O, Y=Z=COOMe
35 X = CH$_2$, Y=Z=H

40

41

42

a X=O, YZ= 
b X=C=CMe$_2$, Y=Z=COOMe
c X=O, Y=Z=COOMe
d X=CH$_2$, Y=Z=H

On the other hand, when these adducts (32–35) were heated at 200 °C for 2 h, 1,4-diphenyltriphenylene (41) was produced by the retrogressive Diels–Alder reaction of the dihydroaromatic intermediates 40 derived by decarbonylation of the initially formed 1:1 adducts (Scheme IV).

With Electron-Deficient Olefins. Recently, Ried et al.[9] reported that the cycloaddition of phencyclone (2) with a electron-deficient *N*-phenyltriazoline-3,5-dione (43) gave the endo [4 + 2] adduct 44 in quantitative yield. We have also investigated the cycloaddition of phencyclone (2) with electron-deficient olefins; equimolar amounts of 2 and 7 and 45–49 were treated to give the 1:1 adducts, 8 and 52–56, in high yields. Similarly, equimolar amounts of 2 and 50 or 51 were treated to give the decarbonylated product 57 or 58. The reaction conditions for these cycloadditions are summarized in Table V. The NMR spectral data are summarized in Table VI.

The adduct 52 is unstable since heating of 52 at below 65 °C afforded 2 and tetracyanoethylene (45) by the retro-

Table III. Reaction Conditions for the Cycloadditions of Phencyclone (2) with Electron-Rich Olefins

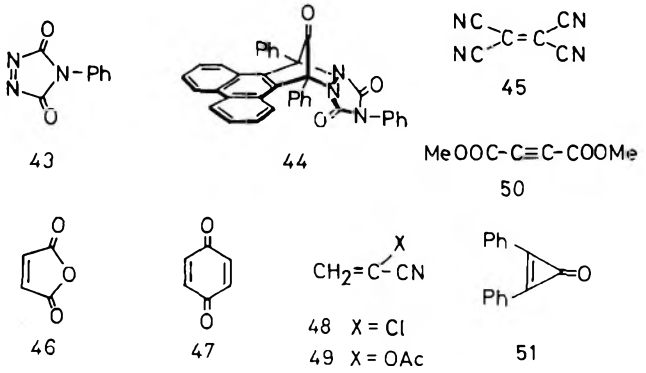
Olefins	Mole ratio (2:olefins)	Reaction conditions (in a sealed tube under argon)		Products (%)
26	1:1	130 °C	7 h	32 (80)
27	1:1	100 °C	5 h	33 (90)
28	1:1	80 °C	2 h	34 (86)
29	1:2.5	80 °C	1.5 h	35 (93)
30	1:1	80 °C	1 h	36 (92)
31	1:1	110 °C	3 h	37 (74)

Table V. Reaction Conditions for the Cycloadditions of Phencyclone (2) with Electron-Deficient Olefins

Olefins	Mole ratio (2: olefin)	Reaction conditions[a]		Product (%)
7	1:1	70 °C	10 min	8 (91)
45	1:1	60 °C	30 min	52 (87)
46	1:1	80 °C	20 min	53 (90)[b]
47	1:1	80 °C	20 min	54 (93)
48	1:1	80 °C	1.5 h	55 (94)
49	1:1	80 °C	2.0 h	56 (80)
50	1:1	90 °C	17 h	57 (81)
51	1:1	150 °C	80 h	58 (29)

[a] In sealed tube under argon. [b] The yield of 95% in benzene at room temperature for 3 h.

Chart IV

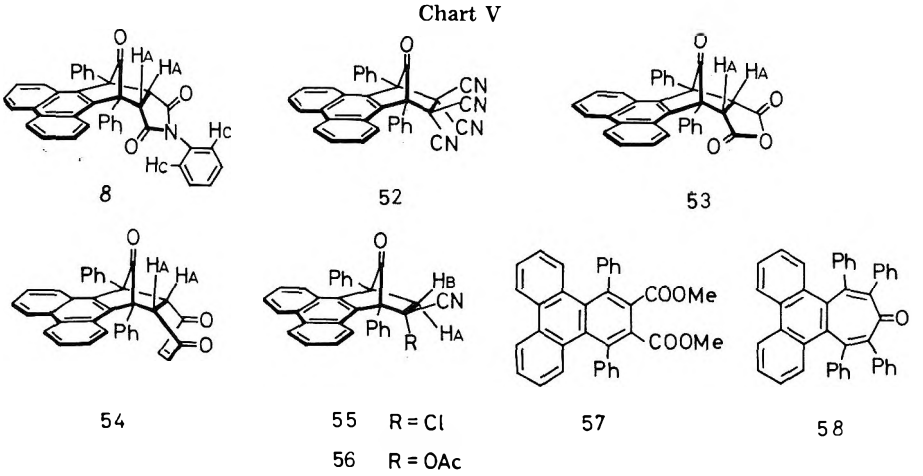


43 44 45 50 46 47 48 X = Cl 49 X = OAc 51

Diels–Alder reaction, but heating in the presence of methanol gave compound 59, presumably via the initial zwitterionic intermediate 60 which was trapped with methanol to give 59.

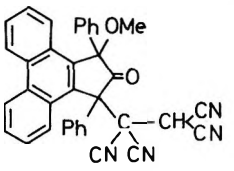
Hydrolysis of the adduct 55 with potassium hydroxide in Me$_2$SO gave compound 64 instead of an expected diketone

Chart V

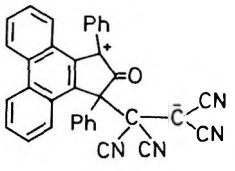


8 52 53 54 55 R = Cl 56 R = OAc 57 58

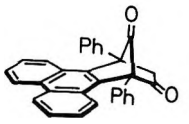
Chart VI



59



60



61

compound **61**. Similar hydrolysis of the adduct **56** gave also the same product **64**.

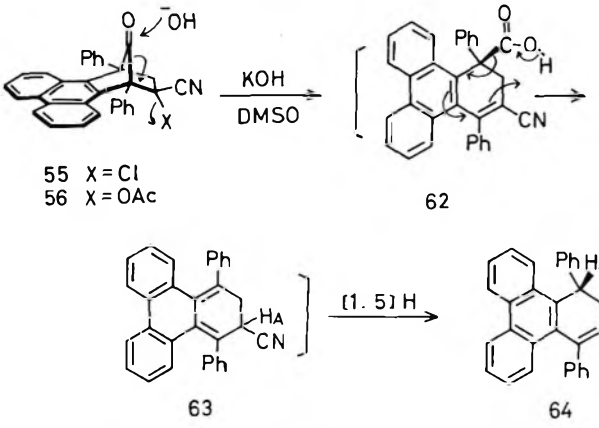
The ir spectrum of **64** showed a characteristic band at 2210 cm^{-1} due to a cyano group, but no carbonyl band. The NMR spectrum of **64** exhibited signals at δ 3.15 (m, 2 H, H_B) and 4.90 (dd, 1 H, J = 6.0 and 3.5 Hz, H_A). These results suggest that ring carbonyl groups of compounds **55** and **56** are very labile in alkaline hydrolysis and they are attacked by a hydroxide anion followed by elimination of leaving groups, i.e., chloro anion or acetoxy anion which locate a trans configuration for the ring carbonyl group.

Finally, an intermediate unstable quinodimethane (**63**) is rearranged by [1.5] hydrogen shifts, which are thermally allowed, to give resonance-stabilized product **64** (Scheme V).

The configurations of the adducts 8 and **52–58** were assigned by the NMR spectra as shown in Table VI.

The NMR spectrum showed the aromatic protons (H_C) at δ 5.87 for 8 and the olefinic protons at δ 5.77 for **54**, which might be shielded owing to lying over the phenanthrene ring.[10] Thus, it is concluded that both adducts 8 and **54** were assigned the endo configuration.

Scheme V



55 X = Cl
56 X = OAc

62

63

64

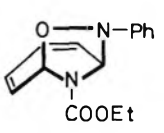
Discussion

It is well known[6,11] that 2,5-dimethyl-3,4-diphenylcyclopentadienone (**1**, R = Ph; R′ = Me) adds thermally to seven-membered ring unsaturated compounds, i.e., tropone, cycloheptatriene, and *N*-carbethoxyazepine, and some dienophiles to give [6 + 4] and [4 + 2] adducts followed by sigmatropic rearrangement products, respectively. However, many other cyclopentadienones, i.e., tetracyclone, acecyclone, indanocyclone, and phenalenocyclone, have not given any adducts with medium-membered ring unsaturated compounds in the cycloaddition reactions. Furthermore, these monomerous cyclopentadienones add to some olefinic dienophiles to give [4 + 2] adducts,[12] which are generally thermally unstable to give the decarbonylated products. However, as described above, phencyclone (**2**) is much more reactive than these cyclopentadienones in the cycloaddition reactions, and the adducts are relatively stable.

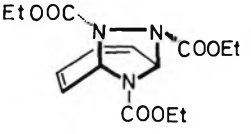
The cycloaddition of phencyclone (**2**) with tropone (**3**) gave the regio- and stereospecific exo [6 + 4] adduct **4**, which might be controlled by the secondary-orbital and the dipole–dipole interaction between the reactants in the transition state. On the other hand, the cycloaddition of **2** with cycloheptatriene (**10**) gave the regio- and stereospecific endo [4 + 2] adduct **11** under heating at 80 °C, while under heating at 170 °C for 20 h, the adduct **11** gave a mixture of a [1.5] sigmatropic rearrangement product (exo [6 + 4] adduct **15**) and a decarbonylated product **14**. However, any [3.3] sigmatropic rearrangement (Cope rearrangement) products were not detected in the cycloadditions of **2** with **3** or **10**. Such rearrangement in **4** and **11** might be energetically unfavorable because of destruction of the aromaticity in the fused phenanthrene ring.

On the other hand, the cycloaddition of phencyclone (**2**) to *N*-carbethoxyazepine (**18**) gave only a formal [6 + 2] adduct **19** without formation of an expected [4 + 2] adduct **20**. By contrast, nitrosobenzene is known to be susceptible to nucleophilic attack of the azepine (**18**) to give a formal [6 + 2] adduct **65**,[13] whereas reaction of *trans*-diethyl azodicarboxylate to the azepine (**18**) gave a formal [6 + 2] adduct **66**,[14] which has been explained to proceed via a nonconcerted fashion by influence of steric factors. Furthermore, high reactivity and stereospecificity were observed in the cycloaddition reactions of **2** with olefinic dienophiles.

Chart VII



65



66

In order to account for the formation of sterespecific endo [4 + 2] isomers in the cycloadditions of **2**, we have considered some common interactions such as secondary-orbital,[3] geometrical primary effect,[15] steric, and dipole–dipole interactions[16] between reactants.

It is clear that the secondary-orbital interactions would be favorable to endo addition in the transition state of the [4 + 2] cycloaddition, and the geometrical primary interactions would be also favorable to endo addition of monolefinic dienophiles like norbornyl compounds (**26–29**), in particular.

Similarly, the dipole–dipole interactions and the steric factors between the "X" portion of the dienophiles and the carbonyl group of **2** would be also favorable to endo approach ([B] and [C]) as depicted in Figure 1. In the absence of the dipole–dipole interactions, the secondary-orbital and steric effects controlled the stereospecificity. This was illustrated with *p*-benzoquinone where the endo adduct was the predominant product. Additionally, it is to be noted that phencyclone (**2**) reacted with both electron-rich and electron-deficient olefins in high yields. Furthermore, it is found that phencyclone was readily trapped by electron-deficient olefins rather than by electron-rich olefins in the Diels–Alder reactions as shown in Tables III and V. Houk et al.[17,18] have recently shown that consideration of frontier orbital analyses can provide a good rationalization of reactivity, regioselectivity, and periselectivity in a variety of cycloaddition reactions,[17] and also estimated frontier orbital energies and coefficients of cyclopentadienone as shown in

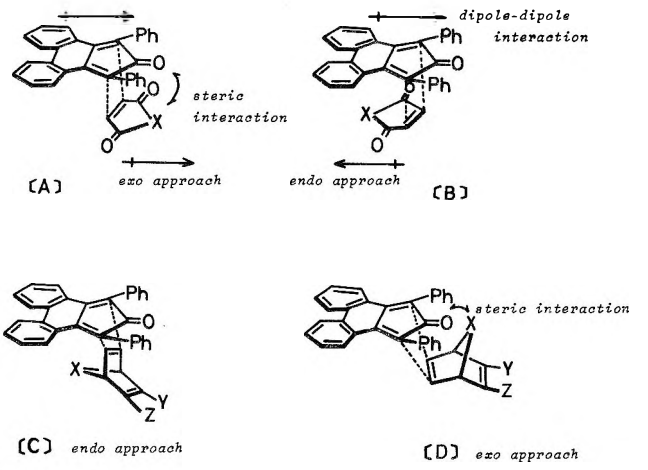


Figure 1.

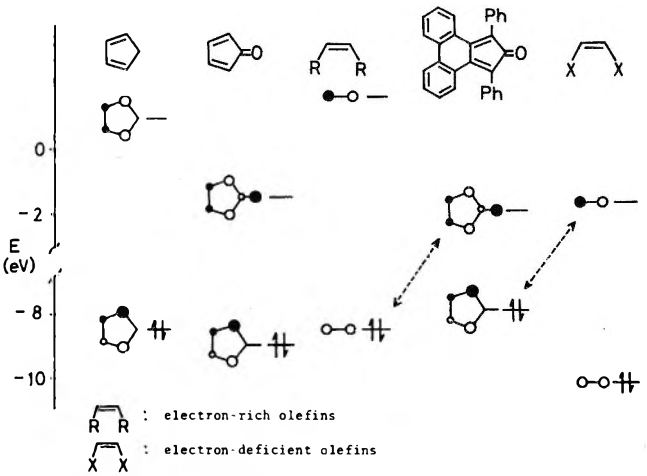


Figure 2. Estimated frontier orbital energies and coefficients for cyclopentadienone and related compounds, and olefins.

Figure 2.[18] In the light of these very low LUMO (lowest unoccupied molecular orbital) energies, cyclopentadienones should be more readily trapped by electron-rich dienophiles than by electron-deficient compounds.[17] However, it is also expected that phencyclone (2) has lower energy LUMO and higher energy HOMO (highest occupied molecular orbital), which has two phenyl groups and a fused phenanthrene ring.

In general, the electron-rich olefins have relatively higher LUMO and HOMO energy levels; on the contrary, the electron-deficient olefins have relatively lower LUMO and HOMO energy levels. Therefore, both interactions of phencyclone HOMO–electron-deficient olefin LUMO (phencyclone HO-controlled) and phencyclone LUMO–electron-rich olefin HOMO (phencyclone LU-controlled) are expected as depicted in Figure 2.

From our experimental results, it is suggested that the interaction between the phencyclone HOMO and electron-deficient olefin LUMO are stronger than the interaction between the phencyclone LUMO and electron-rich olefin HOMO. A more theoretical molecular orbital calculations for these compounds will be presented in the near future.

Experimental Section

The melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. The uv spectra were determined with a Jasco ORD-UV-5 spectrometer. The NMR spectra were taken with a JOEL C-60-XL spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The ir spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer. Mass spectra were obtained with a Hitachi RMU-D double-focusing spectrometer operating at an ionization potential of 70 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 100–150 °C.

Reaction of Phencyclone (2) with Tropone (3). A solution of **2** (1.91 g) and **3** (1.06 g) in benzene (20 ml) was heated at 80 °C under argon in a sealed tube for 20 h. The solution was diluted with methanol (10 ml) and the precipitated solids were filtered off and recrystallized from benzene–methanol to give **4** (1.71 g, 70%) as colorless cubics: mp 235–236 °C dec; ir (KBr) 1780, 1725, and 1605 cm^{-1}.

Anal. Calcd for $C_{36}H_{24}O_2 \cdot C_6H_6$: C, 89.0; H, 5.35. Found: C, 89.1; H, 5.5.

Hydrogenation of 4. A solution of **4** (0.2 g) in ethyl acetate (60 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure to give the tetrahydro compound **6** (0.18 g) as leaflets: mp > 300 °C (chloroform–methanol); ir (KBr) 1778, 1718, and 1505 cm^{-1}.

Anal. Calcd for $C_{36}H_{28}O_2$: C, 87.75; H, 5.75. Found: C, 87.45; H, 5.6.

Reaction of 4 with *N*-Phenylmaleimide (7). A solution of **4** (0.12 g) and **7** (0.085 g) in chlorobenzene (5 ml) was heated at 130 °C under argon in a sealed tube for 2 h. The solution was then evaporated under reduced pressure and chromatographed on silica gel using chloroform as an eluent. The first fractions gave **8** (0.11 g, 80%) as colorless crystals: mp 295–297 °C dec (benzene–methanol); ir (KBr) 1800, 1705, 1600, and 1510 cm^{-1}.

Anal. Calcd for $C_{39}H_{25}O_3N$: C, 84.3; H, 4.55; N, 2.5. Found: C, 84.4; H, 4.75; N, 2.35.

The second fractions gave **9** (0.05 g, 75%) as colorless crystals, mp 235–236 °C (benzene–chloroform).

Reaction of 2 with Cycloheptatriene (10). A solution of **2** (1.91 g) and **10** (4.6 g, 10 mol) in benzene (20 ml) was heated at 80 °C under argon in a sealed tube for 16 h. The solvent was then evaporated under reduced pressure and the residue was chromatographed on silica gel using benzene to give **11** (1.34 g, 57%) as colorless crystals: mp 248–249 °C dec (chloroform–methanol); ir (KBr) 1790, 1600, and 1500 cm^{-1}.

Anal. Calcd for $C_{36}H_{26}O$; C, 91.1; H, 5.5. Found: C, 91.15; H, 5.55.

Hydrogenation of 11. A solution of **11** (0.2 g) in ethyl acetate (50 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure to give the tetrahydro compound **13** (0.19 g) as colorless needles: mp 304–305 °C dec (chloroform–methanol); ir (KBr) 1790, 1605, 1505, and 1450 cm^{-1}.

Anal. Calcd for $C_{36}H_{30}O$: C, 90.35; H, 6.3. Found: C, 90.3; H, 6.35.

Pyrolysis of 11. A solution of **11** (0.15 g) in chlorobenzene (5 ml) was heated at 170 °C under argon in a sealed tube for 20 h. The solvent was then evaporated under reduced pressure and the residue was chromatographed on silica gel using *n*-hexane–benzene (4:1). The first fractions gave **14** (0.05 g, 34%) as colorless cubics: mp 221–222 °C (ether–methanol); ir (KBr) 1600, 1490, and 1440 cm^{-1}

Anal. Calcd for $C_{35}H_{26}$: C, 94.15; H, 5.85. Found: C, 93.9; H, 6.0.

The second fractions gave **15** (0.07 g, 47%) as colorless prisms: mp 274–275 °C dec (chloroform–methanol); ir (KBr) 1768, 1600, 1500, and 1448 cm^{-1}.

Anal. Calcd for $C_{36}H_{26}O$: C, 91.1; H, 5.5. Found: C, 91.2; H, 5.65.

Hydrogenation of 14. A solution of **14** (0.02 g) in ethyl acetate (20 ml) was hydrogenated over 10% Pd/C (0.01 g) under atmospheric pressure to give the dihydro compound **16** (0.02 g) as colorless needles: mp 191–192 °C (ether–methanol); ir (KBr) 1600, 1495, 1440 cm^{-1}.

Anal. Calcd for $C_{35}H_{28}$: C, 93.7; H, 6.3. Found: C, 93.6; H, 6.4.

Hydrogenation of 15. Similar hydrogenation of **15** gave the tetrahydro compound **17** (quantitative) as colorless leaflets: mp 305–307 °C (chloroform–methanol); ir (KBr) 1760, 1600, 1500, 1448 cm^{-1}.

Anal. Calcd for $C_{36}H_{30}O$: C, 90.35; H, 6.3. Found: C, 90.2; H, 6.5.

Reaction of 2 with *N*-Carbethoxyazepine (18). A solution of **2** (0.695 g) and **18** (0.3 g) in benzene (20 ml) was heated at 55 °C under argon in a sealed tube for 20 h, the deep-green color fading. The solvent was then evaporated under reduced pressure and the residue was recrystallized from chloroform–methanol to give the adduct **19** (0.94 g, quantitative) as colorless cubics: mp 251–252 °C; ir (KBr) 1700, 1640, 1600 cm^{-1}; *m/e* 547 (M^+), 382, 165, 92, 65.

Anal. Calcd for $C_{38}H_{29}O_3N$: C, 83.35; H, 5.35; N, 2.55. Found: C, 83.3; H, 5.5; N, 2.6.

Hydrogenation of 19. A. A solution of **19** (0.15 g) in ethyl acetate (50 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure. The reaction mixture was separated by preparative thin layer chromatography on silica gel using chloroform to give the dihydro compound **22** (0.11 g, 73%) as colorless cubics, mp >300 °C (benzene–methanol), and the tetrahydro compound **23** (0.024 g, 15%) as colorless cubics, mp >300 °C (chloroform–methanol).

22: ir (KBr) 1690, 1635, 1600 cm^{-1}.

Anal. Calcd for $C_{38}H_{31}O_3N$: C, 83.05; H, 5.7; N, 2.55. Found: C, 82.8; H, 5.9; N, 2.55.

23: ir (KBr) 1685, 1635, 1600, 1490 cm^{-1}; *m/e* 551 (M^+), 384, 382.

Anal. Calcd for $C_{38}H_{33}O_3N$: C, 82.75; H, 6.05; N, 2.55. Found: C, 82.8; H, 6.15; N, 2.5.

B. A solution of **19** (0.15 g) in ethyl acetate (50 ml) containing acetic acid (1.5 ml) was hydrogenated over Adams catalyst under atmospheric pressure to give the tetrahydro compound **23** (0.15 g, quantitative).

Acid Hydrolysis of 23. To a suspension of **23** (0.15 g) in methanol (30 ml) was added concentrated hydrochloric acid (2 ml) and the solution was refluxed for 5 h. The solvent was then evaporated under reduced pressure and the residue was diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and then the residue was chromatographed on silica gel using benzene–chloroform (1:1) to give **24** (0.13 g, 83%) as a colorless, amorphous solid: ir (neat) 3400, 1745, 1680, and 1610 cm^{-1}.

Anal. Calcd for $C_{38}H_{35}O_4N$: C, 80.1; H, 6.2; N, 2.45. Found: C, 80.15; H, 6.45; N, 2.15.

Cycloaddition Reactions of Phencyclone (2) with Dienophiles. General Procedure for Cycloaddition. A solution of phencyclone (**2**) and an equimolar or excess amount of olefins was heated under argon in a sealed tube until the deep-green color had faded away. The cooled mixture was diluted with methanol and the precipitated solid was filtered off and purified by recrystallization.

With Oxabenzonorbornadiene (26). A solution of **2** (1.67 g) and **26** (0.63 g) in chlorobenzene (25 ml) was heated at 130 °C under argon in a sealed tube for 7 h. The cooled mixture was diluted with methanol and the precipitated solid was filtered off and recrystallized from chloroform–ethanol to give the adduct **32** (1.85 g, 80%) as colorless needles: mp 254–256 °C dec; ir (KBr) 1795, 1600, 1505, 1450 cm^{-1}.

Anal. Calcd for $C_{39}H_{26}O_2$: C, 88.95; H, 5.0. Found: C, 88.7; H, 5.25.

With Dimethyl 7-Isopropylidenenorbornadiene-1,2-dicarboxylate (27). A solution of **2** (0.382 g) and **27** (0.248 g) in chlorobenzene (10 ml) was heated at 100 °C under argon in a sealed tube for 5 h. Then work-up gave **33** (0.57 g, 90%) as colorless needles: mp 241–242 °C dec (benzene–methanol); ir (KBr) 1790, 1720, 1620, 1605 cm^{-1}.

Anal. Calcd for $C_{43}H_{34}O_5$: C, 81.9; H, 5.45. Found: C, 81.75; H, 5.6.

With Dimethyl 7-Oxanorbornadiene-1,2-dicarboxylate (28). A solution of **2** (1.53 g) and **28** (0.84 g) in chlorobenzene (20 ml) was heated at 80 °C under argon in a sealed tube for 2 h. Then work-up gave **34** (2.03 g, 86%) as colorless needles: mp 233–234 °C dec (ethyl acetate–chloroform); ir (KBr) 1800, 1720, 1710, 1630 cm^{-1}.

Anal. Calcd for $C_{39}H_{28}O_6$: C, 79.05; H, 4.75. Found: C, 79.3; H, 4.95.

With Norbornadiene (29). A solution of **2** (0.5 g) and **29** (0.3 g) in chlorobenzene (5 ml) was heated at 80 °C for 1.5 h. Work-up gave **35** (0.58 g, 93%) as colorless crystals: mp 233–234 °C dec (ethyl acetate–methanol); ir (KBr) 1795, 1610, 1510, 1445 cm^{-1}.

Anal. Calcd for $C_{36}H_{26}O$: C, 91.1; H, 5.5. Found: C, 91.25; H. 5.55.

With Acenaphthylene (30). A solution of **2** (0.955 g) and **30** (0.38 g) in toluene (15 ml) was heated at 80 °C for 1 h. Similar work-up gave **36** (1.23 g, 92%) as colorless needles: mp >300 °C (benzene–ethanol); ir (KBr) 1795, 1610, 1505 cm^{-1}.

Anal. Calcd for $C_{41}H_{26}O$: C, 92.1; H, 4.9. Found: C, 92.2; H, 5.15.

With 6,6-Dimethylfulvene (31). A solution of **2** (0.955 g) and **31** (0.265 g) in chlorobenzene (8 ml) was heated at 110 °C for 3 h. Similar work-up gave **37** (0.9 g, 74%) as colorless needles: mp 231–232 °C dec (benzene–methanol); ir (KBr) 1782, 1600, 1500, 1450 cm^{-1}.

Anal. Calcd for $C_{37}H_{28}O$: C, 90.95; H, 5.8. Found: , 91.0; H, 5.8.

With *N*-Phenylmaleimide (7). A solution of **2** (1.91 g) and **7** (0.865 g) in chlorobenzene (25 ml) was heated at 70 °C for 10 min. Similar work-up gave **8** (2.5 g, 91%) as colorless crystals, mp 295–297 °C dec (benzene–methanol).

With Tetracyanoethylene (45). A solution of **2** (0.955 g) and **45** (0.32 g) in benzene (8 ml) was heated at 60 °C for 30 min. Similar work-up gave **52** (1.15 g, 90%) as colorless prisms: mp 221–223 °C dec (benzene); ir (KBr) 2240, 1800, 1600, 1500, 1480 cm^{-1}.

Anal. Calcd for $C_{35}H_{18}ON_4 \cdot \frac{1}{2}C_6H_6$: C, 83.05; H, 3.85; N, 10.2. Found: C, 83.05; H, 4.1; N, 10.25.

On the other hand, the precipitated crystals **52** were recrystallized from methanol–ethyl acetate to give compound **59** (quantitative) as colorless needles: mp 240–242 °C dec; ir (KBr) 1730, 1505, 1450 cm^{-1}; NMR ($CDCl_3$) δ 3.17 (s, 3 H, OMe), 7.0–8.9 [m, 19 H, aromatic H and C**H**$(CN)_2$].

Anal. Calcd for $C_{36}H_{22}O_2N_4$: C, 79.7; H, 4.1; N, 10.35. Found: C, 79.45; H, 4.4; N, 10.2.

With Maleic Anhydride (46). A. A solution of **2** (1.19 g) and **46** (0.49 g) in benzene (20 ml) was heated at 80 °C for 20 min. Similar work-up gave **53** (2.21 g, 92%) as colorless needles: mp 296–298 °C dec (benzene–acetone); ir (KBr) 1865, 1790, 1758, 1605, 1500, 1455 cm^{-1}.

Anal. Calcd for $C_{33}H_{20}O_4$: C, 82.5; H, 4.2. Found: C, 82.6; H, 4.45.

B. A solution of **2** (0.955 g) and **46** (0.245 g) in benzene (20 ml) was stirred at room temperature for 3 h. Similar work-up gave **53** (1.2 g, quantitative).

With *p*-Benzoquinone (47). A solution of **2** (1.91 g) and **47** (0.54 g) in chlorobenzene (20 ml), was heated at 80 °C for 20 min. Similar work-up gave **54** (2.28 g, 93%) as colorless crystals: mp 272–273 °C dec (chloroform–methanol); ir (KBr) 1800, 1680, 1610, 1510, 1455 cm^{-1}.

Anal. Calcd for $C_{35}H_{22}O_3 \cdot \frac{1}{2}H_2O$; C, 84.15; H, 4.65. Found: C, 84.1; H, 4.8.

With 1-Chloroacrylonitrile (48). A solution of **2** (0.955 g) and **48** (0.22 g) in toluene (10 ml) was heated at 80 °C for 1.5 h. Similar work-up gave **55** (1.1 g, 94%) as colorless cubics: mp 176–178 °C dec (dichloromethane–methanol); ir (KBr) 1800, 1600, 1505, 1450, 1440 cm^{-1}.

Anal. Calcd for $C_{32}H_{20}ONCl \cdot \frac{1}{2}CH_2Cl_2$: C, 76.15; H, 4.15; N, 2.75. Found: C, 75.9; H, 4.3; N, 2.8.

With 1-Acetoxyacrylonitrile (49). A solution of **2** (1.91 g) and **49** (0.555 g) in chlorobenzene (18 ml) was heated at 80 °C for 2 h. Similar work-up gave **56** (1.97 g, 80%) as colorless needles: mp 258–260 °C dec (chloroform–methanol); ir KBr) 1800, 1760, 1600, 1500 cm^{-1}.

Anal. Calcd for $C_{34}H_{23}O_3N$: C, 82.75; H, 4.7; N, 2.85. Found: C, 82.95; H, 4.95; N, 2.85.

With Dimethyl Acetylenedicarboxylate (50). A solution of **2** (0.955 g) and **50** (0.355 g) in toluene (10 ml) was heated at 80 °C for 17 h. Similar work-up gave **57** (1.0 g, 81%) as light-green cubics: mp 272–273 °C (ethyl acetate–methanol); ir (KBr) 1750, 1740, 1600, 1500 cm^{-1}.

Anal. Calcd for $C_{34}H_{24}O_4$: C, 82.25; H, 4.85. Found: C, 81.95; H, 4.85.

With Diphenylcyclopropenone (51). A solution of **2** (0.955 g) and **51** (0.515 g) in chlorobenzene (18 ml) was heated at 150 °C for 80 h. Similar work-up gave **58** (0.4 g, 29%) as colorless needles: mp 264–265 °C (chloroform–methanol); ir (KBr) 1720, 1600, 1495, 1450 cm^{-1}.

Anal. Calcd for $C_{43}H_{28}O \cdot H_2O$: C, 89.25; H, 5.25. Found: C, 89.5; H, 5.3.

Hydrogenation of 37. A solution of **37** (0.17 g) in ethyl acetate (45 ml) was hydrogenated over 10% Pd/C (0.05 g) under atmospheric pressure to give the tetrahydro compound **39** (0.17 g) as colorless needles: mp 255–256 °C dec; ir (KBr) 1780, 1600, 1500, 1450 cm^{-1}; NMR ($CDCl_3$) δ 0.15 (d, 3 H, J = 7.0 Hz, CH_3), 1.14 (d, 3 H, J = 7.0 Hz, CH_3), 1.7–2.95 (m, 5 H, H_B and methylene H), 3.80 (m, 1 H, H_C), 4.4–4.92 (m, 2 H, H_A), 7.0–8.1 (m, 16 H, aromatic H), 8.72 (d, 2 H, J = 8.0 Hz, aromatic H).

Anal. Calcd for $C_{37}H_{32}O$: C, 90.2; H, 6.55. Found: C, 90.5; H, 6.35.

Pyrolysis of Compounds 32–35. General Procedure for Pyrolysis. An adduct was heated at 200 °C for 2 h without solvents and chromatographed on silica gel using *n*-hexane–benzene (3:1) as an eluent.

Pyrolysis of 32. The adduct **32** (0.15 g) was heated at 200 °C for 2 h. Work-up gave **41** (0.105 g, 97%) as colorless needles, mp 230–232 °C (lit.[5] 224–226 °C).

Pyrolysis of 33. The adduct **33** (0.1 g) was heated at 200 °C for 2 h. Work-up gave **41** (0.055 g, 91%) but not isolated compound **42b.**

Pyrolysis of 34. The adduct **34** (0.1 g) was heated at 200 °C for 2 h. Similar work-up gave **41** (0.058 g, 91%) and **42c** (0.015 g).

Hydrolysis of 55. To a solution of **55** (0.47 g) in Me_2SO (10 ml) was added a hot solution of KOH (0.17 g) in water (0.3 ml). The mixture was stirred at room temperature for 16 h, and the reaction mixture was then diluted with water (30 ml). The diluted solution was neutralized with dilute hydrochloric acid and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel using benzene to give **64** (0.2 g, 50%) as colorless leaflets: mp 235–237 °C (dichloromethane–methanol); ir (KBr) 2210, 1605, 1505, 1455 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (m, 2 H, H_B), 4.90 (dd, 1 H, J = 6.0 and 3.5 Hz, H_A), 7.1–8.1 (m, 16 H, aromatic H), 8.70 (d, 2 H, J = 8.5 Hz, aromatic H).

Anal. Calcd for $C_{31}H_{21}N$: C, 91.35; H, 5.2; N, 3.45. Found: C, 91.1; H, 5.05; N, 3.55.

Hydrolysis of 56. To a solution of **56** (0.493 g) in Me_2SO (10 ml) was added a hot solution of KOH (0.17 g) in water (0.3 ml). The mixture was stirred at room temperature for 16 h. Similar work-up gave **64** (0.16 g, 40%).

Supplementary Material Available. Tables I, II, IV, and VI of NMR spectra (4 pages). Ordering information is given on any current masthead page.

Registry No.—**2**, 5660-91-3; **3**, 539-80-0; **4**, 57969-45-6; **6**, 57969-46-7; **7**, 941-69-5; **8**, 58002-01-0; **9**, 58002-02-1; **10**, 544-25-2; **11**, 57969-47-8; **13**, 57969-48-9; **14**, 57969-49-0; **15**, 57969-50-3; **16**, 57969-51-4; **17**, 57969-52-4; **18**, 2955-79-5; **19**, 57969-53-6; **22**, 57969-54-7; **23**, 57969-55-8; **24**, 57969-56-9; **26**, 573-57-9; **27**, 19019-88-6; **28**, 1829-60-3; **29**, 121-46-0; **30**, 208-96-8; **31**, 2175-91-9; **32**, 57969-57-0; **33**, 57969-58-1; **34**, 57969-59-2; **35**, 57969-60-5; **36**, 57969-61-6; **37**, 57969-62-7; **39**, 57969-63-8; **41**, 57969-64-9; **42c**, 4282-33-1; **45**, 670-54-2; **46**, 108-31-6; **47**, 106-51-4; **48**, 920-37-6; **49**, 3061-65-2; **50**, 762-42-5; **51**, 886-38-4; **52**, 36428-90-7; **53**, 57969-65-0; **54**, 57969-66-1; **55**, 57969-67-2; **56**, 57969-68-3; **57**, 57969-69-4; **58**, 57969-70-7; **59**, 57969-71-8; **64**, 57969-72-9.

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Synthesis of β-Lactams via Cycloaddition of Iminodithiocarbonate Esters with Azidoketene[1]

Donald F. Sullivan,[2a] David I. C. Scopes,[2b] Arthur F. Kluge, and John A. Edwards*

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

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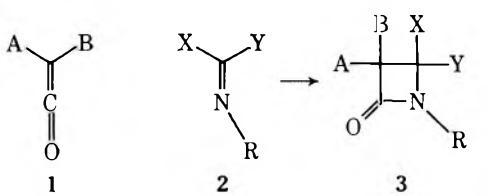
The reaction of iminodithiocarbonate esters with azidoketene afforded β-lactams containing an ortho ester functionality. The yield of cycloaddition is influenced by the steric and electronic nature of the imine substrate and by the order of addition of reagents. The 1,2-secopenam analogs **16b** and **25** were prepared through reaction of imines **15** and **22** with azidoacetyl chloride–triethylamine followed by transformation of the azide function to an acylamido function. Ring opening of the β-lactams was achieved under a variety of conditions: **7a** gave **11** with trifluoroacetic acid, **7b** gave **12** with hog pancreatic lipase, and **16b** and **25** were transformed to **17** and **26**, respectively, with silica gel.

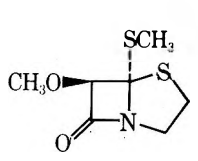
Spurred by the importance of penicillins and cephalosporins to antibiotic therapy, synthetic chemists have devised numerous methods for the preparation of the natural β-lactams and related analogues.[3] One such route, the reaction of ketenes with imines, has proven a versatile method for the synthesis of medicinally important compounds.[4a–e]

We became interested in the ortho ester functionality which would result from the cycloaddition of a ketene with a bishetero-substituted imine (**1** + **2** → **3**). The use of azidoketene in a cycloaddition reaction with a bishetero-substituted imine, besides incorporating the ortho ester functionality, would permit the subsequent introduction of the biologically important *N*-acylamido moiety onto the resultant β-lactams (**1** + **2** → **3**; A = N_3; B = H). Suitable choice of the imine can yield β-lactams containing other functionalities important for biological activity (i.e., R = $CHR'CO_2R''$).



1 **2** **3**

Several examples of β-lactams containing ortho ester functionality have been published. A Bayer group has described 41 β-lactams derived from the reaction of *N*-alkyliminodithiocarbonate dimethyl esters with various ketenes.[5] Bose has prepared the penicillin analogue **4** through the reaction of 2-methylthio-2-thiazoline with methoxyketene.[6] Bose has also described β-lactams of the general type **5** which were derived through the addition of various ketenes, including azidoketene, to N-acylated 2-methylthio-1,4,5,6-tetrahydropyrimidines.[7]



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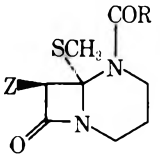

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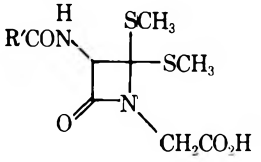
Results and Discussion

The initial target compound **6a** incorporated a glycine residue into the β-lactam. The plan was to prepare acid **6a**



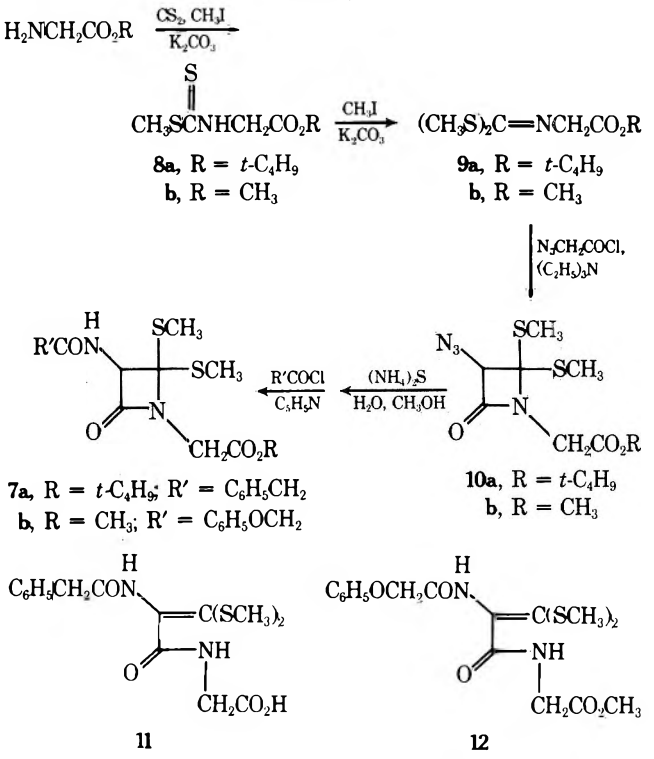
6a, R′ = $C_6H_5CH_2$
b, R′ = $C_6H_5OCH_2$

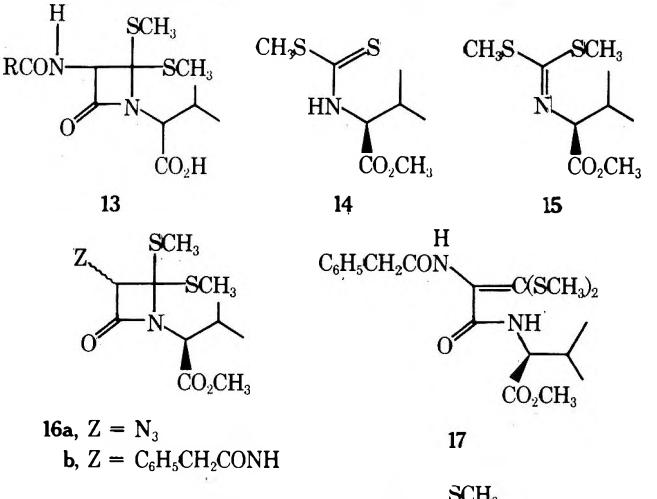
through acid-catalyzed hydrolysis of an ester such as **7a**. Accordingly, glycine *tert*-butyl ester was condensed with carbon disulfide, methyl iodide, and potassium carbonate to give dithiocarbonate **8a** (65%), which was further condensed with methyl iodide to give iminodithiocarbonate dimethyl ester **9a** (89%). Reaction of **9a** with azidoacetyl chloride in the presence of triethylamine (addition of the acid chloride to a solution of iminodithiocarbonate and triethylamine) afforded β-lactam **10a** in quantitative yield based on a 36% conversion of **9a**. The acylamido side chain was introduced by first reducing the azide to the amine with excess ammonium sulfide and then acylating with phenylacetyl chloride–pyridine to give **7a** (58%). Attempted hydrolysis of **7a** with trifluoracetic acid–anisole gave the ring-opened acid **11** instead of the desired acid **6a**.

In order to circumvent the difficulty posed by acid hydrolysis a methyl ester was substituted for the *tert*-butyl ester. Glycine methyl ester was transformed through **8b** (90%) to **9b** (50% from **8b**). Condensation of **9b** with azidoacetyl chloride–triethylamine afforded β-lactam **10b** in 80% yield based on 32% recovered **9b**. The azide **10b** was converted in two steps to the phenoxyacetamido compound **7b** (36%). The initial attempt at hydrolysis of ester **7b** using mild (pH 7) enzymatic conditions[8] gave the ester **12** in 70% yield. Having failed with enzymatic hydrolysis we opted for the more straightforward method of treating **7b** with 1.05 equiv of lithium hydroxide in water at room temperature. The desired acid **6b** was thereby obtained in 60% yield after acidification and work-up. These reactions are summarized in Scheme I.

Having achieved the overall transformation of an amino acid into a β-lactam consistent with the constraints which were originally imposed on functionality, an attempt was made to incorporate a carbon framework more in keeping with that of a penicillin. A molecule such as **13** could be thought of as an opened penicillin analogue (a 1, 2-secopenicillin). L-Valine methyl ester[9] was converted to the dithiocarbonate **14** (76%), which was smoothly transformed to the iminodithiocarbonate **15** (72%) with methyl iodide–sodium hydride in THF. The cycloaddition reaction of **15** with azidoketene was attempted with the usual conditions of addition of 1 equiv of azidoacetyl chloride to a methylene chloride solution of **15** and 1 equiv of triethylamine. This mode of addition gave rise to trace amounts of two new components by TLC analysis; moreover, the amount of these new components did not increase appreciably with the sequential addition of another equivalent of firstly triethylamine and then azidoacetyl chloride. The order of addition was inverted by adding 2 equiv of azidoacetyl chloride followed by 2 equiv of triethylamine. This inverted addition procedure resulted in substantially more of the two new components than did the normal addition procedure. A repeat reaction using the inverted addition procedure with the addition of 4 equiv of triethylamine to a methylene chloride solution of **15** and 4 equiv of azidoacetyl chloride afforded a diastereomeric mixture of β-lactams **16a** in 20% yield based on 34% recovered **15**. The mixture of azides **16a** was transformed into a mixture of phenacylamido β-lactams **16b** in 45% yield by ammonium sulfide reduction followed by acylation of the amine. The diastereomeric mixture **16b** (ca. 2:1 by NMR) could not be resolved into the individual diastereomers by silica gel chromatography. The chromatographic purification of **16b** was accompanied by some ring opening on the silica gel to give **17**.

Scheme I





11 **12**

13 **14** **15**

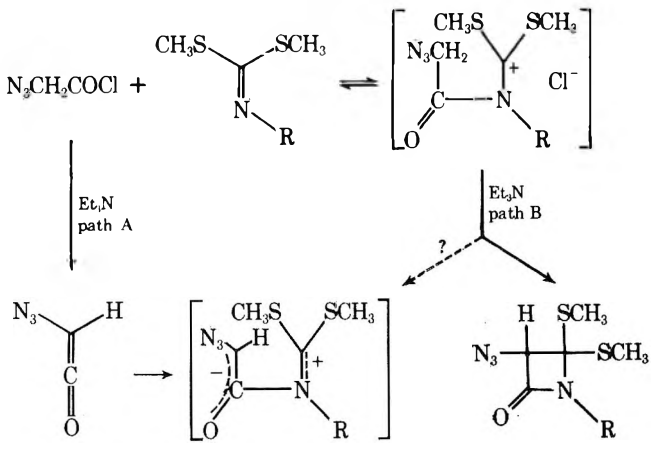
16a, Z = N_3
b, Z = $C_6H_5CH_2CONH$

17

18 **19**

Attempting to explain the relative success of β-lactam formation with various substrates and the relative success

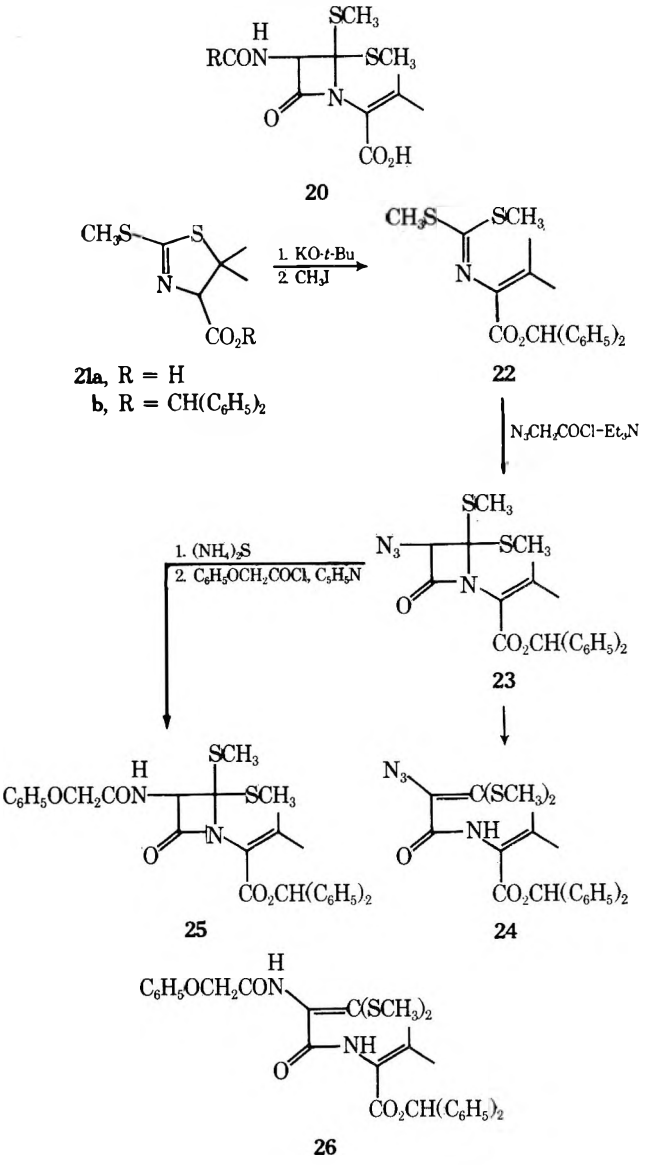
Scheme II



of the normal vs. the inverse addition mode brings up some of the complexities inherent in the mechanism(s) of the cycloaddition reaction (Scheme II). Bose has coined the term "the acid chloride reaction" for a reaction in which the imine and acid chloride are mixed and then triethylamine is added to that mixture to give a β-lactam.[10] In the case studied by Bose it was felt from NMR evidence that a covalently bonded intermediate was formed in a reversible reaction of the acid chloride with the imine, and that β-lactam formation "may entirely by-pass the ketene pathway—at least in those instances where *cis* β-lactams are formed". On the other hand, Ghosez[11] interpreted the normal addition mode (acid chloride added to a solution of imine plus triethylamine) as proceeding primarily through the intermediacy of a ketene which then reacted with an imine to form a heterodiene dipolar intermediate.[12] In Ghosez's case the use of the inverse addition mode by the prior formation of an adduct of benzalaniline with dichloroacetyl chloride and subsequent reaction with triethylamine afforded the β-lactam in much lower yield than that which accompanied the normal addition mode. Such a result may indeed mean that a covalently bonded intermediate may proceed to β-lactam without going through a dipolar intermediate.[13] In our examples we find that if the imine is deactivated by steric or electronic factors, then the inverse addition mode is indicated for a successful reaction. Consistent with this notion of substrate dependence we find that the omission of the carboxylate functionality, which is presumably deactivating through its inductive effect, was beneficial in terms of giving a high yield for β-lactam formation: the iminodithiocarbonate **18** reacted with azidoacetyl chloride by the normal addition procedure to give **19** in 92% yield. One unresolved question which is posed by a successful result obtained through the normal addition mode is whether the product was formed through a ketene pathway (A), or through a prior acylation step followed by proton abstraction and ring closure (B). In the case of a reactive (undeactivated) imine, there is the possibility of exclusive reaction by path B if the imine acylation step could compete in rate with the alternative of ketene formation by proton abstraction from azidoacetyl chloride.

The investigation of systems resembling an open penicillin was extended to the β-lactam **20**. Methylthiothiazoline **21a**[14] was converted to the benzhydryl ester **21b**, which upon treatment with potassium *tert*-butoxide in THF at −65 °C followed by trapping with methyl iodide afforded iminodithiocarbonate **22** (88%). The course of the reaction of **22** with azidoacetyl chloride–triethylamine paralleled that of **15**. Again the inverse addition mode seemed crucial to the success of the cycloaddition. The resulting β-lactam proved to be very unstable to normal silica gel or alumina

Scheme III

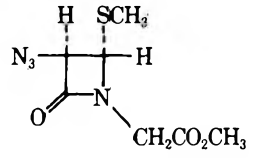


chromatography so recourse was taken to purification through the use of countercurrent distribution,[15] whereby we were able to obtain reasonably pure β-lactam **23** in 61% yield. The decomposition of **23** on silica gel gave the ring-opened material **24**. The purified azide **23** was transformed into the phenoxyacetamido derivative **25** by the normal route. Compound **25** was very difficult to purify and it was obtained in ca. 85% purity with the major impurity being **26**. These reactions are summarized in Scheme III.

A chord struck throughout this study is that of the ring cleavage of these ortho ester type β-lactams. Bose has observed this type of cleavage in the presence of trifluoroacetic acid and suggested that protonation of the amide nitrogen initiated ring opening.[6] Ring opening can then lead to a carbonium ion stabilized by two sulfur substituents. Loss of a proton from this intermediate gives the ring-opened product. In some of our cases a strong acid such as trifluoroacetic acid was not needed, and indeed, silica gel was sufficiently acidic to cleave **16b**, **23**, and **25**.

On a final note we became interested in what effect, if any, the ortho ester functionality exerted on the β-lactam carbonyl infrared stretching frequency. Carbonyl stretching frequencies of β-lactams have been taken as a measure of relative acylating power and have been successfully correlated with biological activity.[16] Comparison of β-lactam carbonyl stretching frequencies for pairs **10b** and **27**[17]

(1785 vs. 1785 cm^{-1}: $CHCl_3$) and **25** and **28**[18] (1775 vs. 1765 cm^{-1}: $CHCl_3$) showed that the ortho ester functionality imparted no consistent effect to the carbonyl stretching frequency. The results of biological testing of compound **29**[17] paralleled the experience of a Beecham group with 1,2-secopenicillin **30**;[19] with both compounds there was no significant antibacterial activity.



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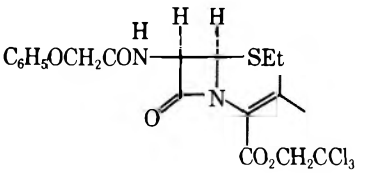

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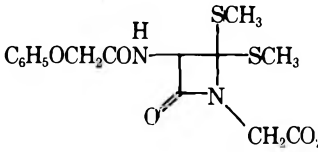

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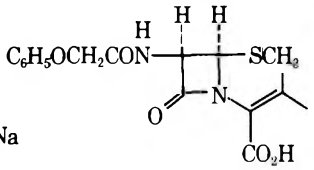

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Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 237B grating spectrometer. NMR spectra, unless noted otherwise, were obtained in deuteriochloroform (ca. 10% w/v) with Me_4Si internal standard using a Varian A-60 or HA-100. Combustion analyses were performed by A. Bernhardt, Mulheim (Ruhr), West Germany, and by our microanalytical laboratory. The mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 70 eV and an acceleration voltage of 3 kV. We gratefully acknowledge Mr. V. Hayashida, Dr. M. Maddox, Mrs. J. Nelson, Mrs. L. Kurz, Dr. L. Tökès, and Mr. J. Smith for their assistance with analytical measurements.

***tert*-Butyl 2-(*S*-Methyldithiocarbamoyl)acetate (8a).** A 500-ml Erlenmeyer flask equipped with a magnetic stirrer was charged with 250 ml of methanol and 7.85 g (50 mmol) of *tert*-butyl azidoacetate. The flask was cooled in a water bath and 80 ml of a 22% ammonium sulfide solution was added in one portion. After 0.5 h, the solution was saturated with sodium chloride and was thoroughly extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and the chloroform was evaporated to give 7.25 g of an oil. The oil was taken up into 75 ml of THF and 7 ml of water and this mixture was added to a 250-ml Erlenmeyer along with 3.33 ml (4.21 g, 55.3 mmol) of carbon disulfide. After 10 min, 3.82 g (27.6 mmol) of potassium carbonate and 8.25 g (3.62 ml, 58 mmol) of methyl iodide were added. After an additional 15 min, the solution was diluted with ca. 150 ml of diethyl ether and was washed with water. The organic layer was collected, dried (Na_2SO_4), and evaporated to give 8 g of crude acetate **8a** (72% from the azide). Recrystallization from acetone–hexane afforded 7.5 g of white crystals: mp 108–112 °C; NMR δ 1.49 [s, 9 H, $C(CH_3)_3$], 2.63 (s, 3 H, SCH_3), 4.35 (d, 2 H, J = 4.5 Hz, $HNCH_2$), 7.25 (broad, 1 H, NH); ir ($CHCl_3$) 3290, 1725, 1520 cm^{-1}. Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.45; H, 6.83; N, 6.33. Found: C, 43.28; H, 6.83; N, 6.25. MS *m/e* 221 (M^+).

Methyl 2-(*S*-Methyldithiocarbamoyl)acetate (8b). Carbon disulfide (4.8 ml, 79.6 mmol) and 75 ml of THF were placed in a 250-ml Erlenmeyer flask equipped with a magnetic stirrer. To this solution were added 10 g (79.6 mmol) of methyl glycinate hydrochloride, 7 ml of water, and 10.9 g (78.9 mmol) of potassium carbonate. After 15 min, 4.95 ml (11.28 g, 79.5 mmol) of methyl iodide was added. The solution was stirred for 0.5 h and was worked up in the same manner as **8a** to give 11.5 g (81%) of an oil which crystallized on standing to give a solid: mp 44–46 °C; NMR δ 2.63 (s, 3 H, SCH_3), 3.79 (s, 3 H, OCH_3), 4.49 (d, 2 H, J = 5 Hz, $HNCH_2$), 7.83 (broad, 1 H, NH); ir (film) 3345, 1745 cm^{-1}. Anal. Calcd for $C_5H_9NO_2S_2$: C, 33.50; H, 5.06; N, 7.81. Found: C, 33.24; H, 5.17; N, 7.73. MS *m/e* 179 (M^+).

Methylation of 2-(*S*-Methyldithiocarbamoyl)acetates. The methyl ester **8b** (10 g, 55.8 mmol) was dissolved in a solution of 75 ml of THF and 7 ml of water, and 3.85 g (27.8 mmol) of potassium carbonate was added to the solution. Methyl iodide (17.5 ml, 280 mmol) was added and the solution was heated at reflux for ca. 15 h. Water (ca. 100 ml) was added and the mixture was extracted with diethyl ether. The ether was dried (Na_2SO_4) and evaporated to an oil. The oil was chromatographed from ca. 200 g of silica gel (3.5:1 hexane–diethyl ether) to give 5.4 g (50%) of the bismethylthioimino acetate **9b** as an oil: NMR δ 2.38 (s, 3 H, SCH_3), 2.53 (s, 3 H, SCH_3), 3.68 (s, 3 H, OCH_3), 4.12 (s, 2 H, NCH_2); ir (film) 1755, 1580 cm^{-1}; *m/e* 193 (M^+). The *tert*-butyl imino acetate **9a** was prepared using 2 equiv of potassium carbonate. The yield of **9a** (oil) was 89% following chromatography from silica gel (6:1 hexane–diethyl ether): NMR δ 1.48 [s, 9 H, $C(CH_3)_3$], 2.43 (s, 3 H, SCH_3), 2.55 (s, 3 H, SCH_3), 4.15 (s, 2 H, NCH_2); ir (film) 1750, 1585 cm^{-1}; *m/e* 235 (M^+). Calcd for $C_9H_{17}NO_2S_2$: C, 45.92; H, 7.28; N, 5.95. Found: C, 45.57; H, 7.31; N, 5.91.

***tert*-Butyl 2-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)-acetate (10a).** A 50-ml round-bottom three-necked flask equipped with an addition funnel, magnetic stirrer, and gas inlet tube was dried and flushed with nitrogen. A solution of **9a** (2.35 g, 10 mmol) in 5 ml of methylene chloride was added to the flask along with 1.39 ml (1.01 g, 10 mmol) of triethylamine. The flask was immersed in a water bath at ca. 30 °C and a solution of 0.89 ml of azidoacetyl chloride in 5 ml of methylene chloride was added dropwise over 1–1.5 h. After the addition was completed, 0.42 ml of triethylamine was added, and then 0.27 ml of azidoacetyl chloride in 2 ml of methylene chloride was added over ca. 1 h. The solvent was evaporated under vacuum, and the residue was chromatographed from ca. 100 g of silica gel with 3:1 hexane–diethyl ether to give 1.13 g (36%) of the oily β-lactam **10a** along with 1.5 g of the imine **9a:** NMR δ 1.49 [s, 9 H, $C(CH_3)_3$], 2.23 (s, 6 H, SCH_3), 3.87 (apparent doublet 2 H, NCH_2), 4.80 (s, 1 H, N_3CH); ir (film) 2120, 1785, 1740 cm^{-1}.

Methyl 2-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)acetate (10b). The method of preparation was similar to that used to prepare **10a.** Here, however, 2 equiv of triethylamine was present initially in solution with the imide **9b.** Upon complete addition of 1 equiv of azidoacetyl chloride, an additional 1 equiv of triethylamine was added to the reaction mixture and a further 1 equiv of azidoacetyl chloride in methylene chloride was added dropwise. Direct chromatography of the mixture afforded 32% recovered **9b** and 55% of the oily β-lactam **10b:** NMR δ 2.23 (s, 6 H, SCH_3), 3.78 (s, 3 H, OCH_3), 3.98 (apparent doublet, 2 H, NCH_2), 4.85 (s, 1 H, N_3CH); ir ($CHCl_3$) 2130, 1785, 1755 cm^{-1}.

Methyl 2-*S*-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)-3-methylbutyrate (16a). L-Valine hydrochloride methyl ester[20] (76 g, 454 mmol) was condensed with carbon disulfide (27.3 ml, 453 mmol) and methyl iodide (28.3 ml, 454 mmol) in THF–water as described for **8b.** The yield of the oily butyrate **14** was 76%: NMR δ 1.00 [two doublets, 6 H, J = 6 Hz, $HC(CH_3)_2$], 2.37 [m, 1 H, $HC(CH_3)_2$], 2.63 (s, 3 H, SCH_3), 3.78 (s, 3 H, OCH_3), 5.27 (dd, 1 H, J = 6, J' = 5 Hz, HNCHCH), 7.63 (broad, 1 H, HN); ir (film) 1740 cm^{-1}; *m/e* 221 (M^+). Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.41; H, 6.83; N, 6.32. Found: C, 43.17; H, 6.88; N, 6.24.

The ester **14** (5.3 g, 24 mmol) along with 2.97 ml of methyl iodide were dissolved in 20 ml of THF under a nitrogen atmosphere in a three-necked, 250-ml flask. Sodium hydride (1.01 g of a 51% mineral oil suspension, 24 mmol) was added in small portions. Vigorous stirring of the mixture, coupled with slow addition of the sodium hydride, was necessary to control the foaming. After 5 min the solution was diluted with 100 ml of diethyl ether and the resulting mixture was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to an oil, which was distilled under vacuum (bp 94 °C, 0.5 mm) to give 4.06 g (72%) of the oily bismethylthioimine **15:** NMR δ 0.92 [two doublets, 6 H, J = 7 Hz, $HC(CH_3)_2$], 2.23 [m, 1 H, $HC(CH_3)_2$], 2.40 (s, 3 H, SCH_3), 2.52 (s, 3 H, SCH_3), 3.68 (s, 3 H, OCH_3), 4.15 (d, 1 H, J = 5.5 Hz, NCHCH); ir (film) 1745, 1582 cm^{-1}; *m/e* 192 ($M^+ - C_3H_7$), 188 ($M^+ - SCH_3$). Anal. Calcd for $C_9H_{17}NO_2S_2$: C, 45.92; H, 7.28; N, 5.95. Found: C, 46.01; H, 7.08; N, 5.73.

The imino ester **15** when treated with triethylamine–azidoacetyl chloride as in the preparations of β-lactams **10a** and **10b** gave only minor amounts of product. Reversal of the order of addition by first mixing **15** with azidoacetyl chloride in methylene chloride, followed by dropwise addition over ca. 1 h of a methylene chloride solution of triethylamine (1 equiv), produced the β-lactam **16a** in ca. 30% yield. The azide **16a** was sensitive to silica gel chromatography, but rapid chromatography using 2.5:1 hexane–diethyl ether gave an oily product with satisfactory spectral properties: NMR δ 0.95, 1.07 [two doublets, 6 H, J = 6.5 Hz, $HC(CH_3)_2$], 2.16, 2.19, 2.23, 2.25 (four singlets, 6 H, SCH_3), 2.69 [m, 1 H, $HC(CH_3)_2$], 3.45

(d, 1 H, J = 9.5 Hz, NCHCH), 3.76 (s, 3 H, OCH_3), 4.54, 4.65 [two singlets, 1 H (relative ratio ca. 2:1), N_3CH]; ir ($CHCl_3$) 2100, 1775, 1740 cm^{-1}.

Reduction and Acylation of 3-Azido-2-azetidones. The β-lactam **10a** (1 g, 3.15 mmol) was dissolved in 15 ml of methanol. Approximately 5 ml of a 22% ammonium sulfide solution was added. After 0.5 h 30 ml of a saturated solution of sodium chloride in water was added, and the resulting mixture was extracted with methylene chloride. After drying over Na_2SO_4, the methylene chloride solution was concentrated to ca. 10 ml. To this solution cooled to 0 °C were added 0.98 g (6.35 mmol) of phenylacetyl chloride and 0.5 g (6.35 mmol) of pyridine. The cooling bath was removed after 15 min and the solution was stirred at room temperature for 45 min. After washing with water, the methylene chloride layer was dried (Na_2SO_4) and evaporated to a residue which was crystallized from acetone–hexane to give 0.76 g (59%) of **7a**: mp 116–117 °C; NMR δ 1.46 [s, 9 H, $C(CH_3)_3$], 1.86 (s, 3 H, SCH_3), 2.63 (s, 3 H, SCH_3), 3.67 (s, 2 H, $C_6H_5CH_2$), 3.82 (s, 2 H, NCH_2), 5.61 (d, 1 H, J = 9.5 Hz, HNC**H**), 6.62 (broad doublet, 1 H, J = 9.5 Hz, **H**NCH), 7.33 (s, 5 H, C_6H_5); ir (KBr) 1790, 1735, 1670 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2O_4S_2$: C, 55.58; H, 6.38; N, 6.82. Found: C, 55.55; H, 6.25; N, 6.65. MS m/e 410 (M^+).

The β-lactams **7b** and **16b** were prepared in identical fashion, with the exception that phenoxyacetyl chloride was substituted for phenylacetyl chloride in the case of **7b**. The yield of the 3-phenoxyacetamidoazetidinone **7b** (mp 89.5–90 °C) was 35%: NMR δ 2.03 (s, 3 H, SCH_3), 2.28 (s, 3 H, SCH_3), 3.79 (s, 3 H, OCH_3), 4.00 (s, 2 H, NCH_2), 4.59 (s, 2 H, OCH_2), 5.70 (d, 1 H, J = 9.5 Hz, HNC**H**), 7.2 (m, 5 H, C_6H_5), 7.78 (broad doublet, 1 H, J = 9.5 Hz, HNCH); ir (KBr) 3350, 1775, 1750, 1685 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_5S_2$: C, 49.98; H, 5.24; N, 7.28. Found: C, 49.86; H, 5.12; N, 7.19. MS m/e 384 (M^+).

The yield of methyl 2-(3-phenylacetamido-4,4-dimethylthio-3-azetidinon-2-yl)-3-methylbutyrate (**16b**) from the azide **16a** was 45%, as a 2:1 mixture of diastereomers: NMR δ 1.15 [apparent triplet, 6 H, $CH(CH_3)_2$], 1.78, 1.90, 2.17, 2.2 (four singlets, 6 H, SCH_3), 2.62 [m, 1 H, $CH(CH_3)_2$], 3.43, 3.47 (two doublets, 1 H, J = 9 Hz, NC**H**CH), 3.63 (s, 2 H, $C_6H_5CH_2$), 3.68, 3.73 (two singlets, 3 H, OCH_3), 5.47 (d, 1 H, J = 9 Hz, HNC**H**), 6.77 (broad, 1 H, **H**NCH), 7.3 (s, 5 H, C_6H_5); ir ($CHCl_3$) 1775, 1745, 1685 cm^{-1}. MS m/e 363 ($M^+ - SCH_3$).

The purification of **16b** was complicated by its sensitivity to silica gel chromatography. A rearranged product **17** was obtained: NMR δ 1.02 [two doublets, 6 H, J = 6.5 Hz, $CH(CH_3)_2$], 2.14 (s, 3 H, SCH_3), ca. 2.2 [m, 1 H, $HC(CH_3)_2$], 2.25 (s, 3 H, SCH_3), 3.67 (s, 2 H, $C_6H_5CH_2$), 3.75 (s, 3 H, OCH_3), 4.66 (dd, 1 H, J_1 = 8, J_2 = 4 Hz, HNCHCH), 6.72 (broad, 1 H, HN), 7.33 (s, 5 H, C_6H_5), 7.62 (broad, 1 H, HN); ir ($CHCl_3$) 1725, 1655 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2O_4S_2$: C, 55.58; H, 6.38; N, 6.82. Found: C, 55.32; H, 6.46; N, 6.87.

Methyl 2-(3-Azido-4-methylthio-2-azetidinon-1-yl)acetate (27). Glycine (10 g, 133 mmol) was added to 37 ml of formic–acetic anhydride at 0 °C. After 1 min a precipitate formed. This was collected by filtration and was recrystallized from methanol to give 12.87 g (94%) of *N*-formylglycine, mp 140–150 °C dec. An ethereal solution of excess diazomethane at 0 °C was added to 7.5 g (72.8 mmol) of the *N*-formylglycine. Upon dissolution of the acid, the solution remained at 0 °C for 1 h. The solution was allowed to warm to room temperature and set aside until the yellow color of diazomethane had disappeared. The ether was decanted from an oily residue and was evaporated to give a crude product. This product was distilled under vacuum to give 6.1 g (72%) of methyl *N*-formylglycinate (bp 100 °C, 1 mm): NMR ($CDCl_3$) δ 3.75 (s, 3 H, OCH_3), 4.08 (d, 2 H, J = 5.5 Hz, HNCH_2), 7.08 (broad, 1 H, HN), 8.25 (s, 1 H, HCO); ir (film) 1750, 1675 cm^{-1}.

The methyl *N*-formylglycinate (2.5 g, 21.4 mmol) was dissolved in 25 ml of dry THF and to this solution was added 7 g (31.5 mmol) of phosphorus pentasulfide. After 0.5 h, the mixture was filtered and the yellow solid was washed with ethyl acetate. The combined filtrate and washings was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give an oil. This crude product was chromatographed from ca. 200 g of silica gel with chloroform. Methyl *N*-thioformylglycinate, mp 45–48 °C, was obtained in 54% yield (1.53 g): NMR δ 3.80 (s, 3 H, OCH_3), 4.45 (d, 2 H, J = 5 Hz); ir (KBr) 1730 cm^{-1}. Anal. Calcd for $C_4H_7NO_2S$: C, 36.07; H, 5.30; N, 10.52. Found: C, 35.86; H, 5.39; N, 10.22.

Methyl *N*-thioformylglycinate (5 g, 37.6 mmol), potassium carbonate (5.71 g, 41.4 mmol), and methyl iodide (2.8 ml, 45 mmol) were mixed with 10 ml of acetone under nitrogen and stirred at room temperature for 24 h. Water (50 ml) was added, and the mixture was extracted with diethyl ether. The ether extracts were combined and dried (Na_2SO_4). Evaporation of the ether and distillation afforded 2.1 g (38%) of an oil (bp 72 °C, 1.5 mm) whose spectral data were consistent with a mixture of *syn*- and *anti*-methyl 2-(methylthioimino)acetate diastereomers: NMR δ 2.40, 2.53 (two singlets, 3 H, SCH_3) 3.73, 3.78 (two singlets 3 H, OCH_3), 4.08, 4.27 (doublet and singlet, 2 H, J = 2 Hz, SCH=NCH_2), 8.30 (m, 1 H, HC=N); ir (film) 1755, 1605 cm^{-1}. MS m/e 147 (M^+).

The usual procedure of adding azidoacetyl chloride to the methylene chloride solution of imine and triethylamine was used, incorporating 2 equiv of the acid chloride and amine. Starting with 0.5 g of the methylthioimine, a 70% yield of the trans β-lactam **27** was realized: NMR δ 2.01 (s, 3 H, SCH_3), 3.72, 4.30 two doublets, 2 H, J = 18 Hz, NCH_2), 3.78 (s, 3 H, OCH_3), 4.57 (d, 1 H, J = 2 Hz, SCH), 4.78 (d, 1 H, J = 2 Hz, N_3CH); ir ($CHCl_3$) 1785, 1755 cm^{-1}. MS m/e 231 ($M^+ + 1$), 229 ($M^+ - 1$). The azide failed to give a satisfactory combustion analysis. The corresponding 3-phenylacetamido-2-azetidinone was prepared via reduction of the azide **27** with ammonium sulfide, followed by acetylation with phenylacetyl chloride, as in the preparation of **7a**. The methyl 2-(*trans*-3′-phenylacetamide-4′-methylthio-2′-azetidinon-1′-yl)acetate was purified using column and thin layer chromatography, and crystallized after prolonged standing at room temperature: mp 87.5–88.5 °C; NMR δ 2.08 (s, 3 H, $-SCH_3$), 3.58 (s, 2 H, $PhCH_2CONH$), 3.70 (s, 3 H, $-CO_2CH_3$), 3.71 (d, 1 H, J = 18 Hz, $-NCH_2CO_2CH_3$), 4.20 (d, 1 H, J = 18 Hz, $NCH_2CO_2CH_3$), 4.71 (d, 1 H, J = 2 Hz, $-CHSCH_3$), 4.92 (d of d, 1 H, J = 2, 8 Hz, O=CNHC**H**), 6.58 (broad signal, 1 H, –CONH–), 7.27 (s, 5 H, $-C_6H_5$); ir ($CHCl_3$) 1775, 1745, 1680 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.62; N, 8.68. Found: C, 55.76; H, 5.81; N, 8.28.

Rearrangement of *tert*-Butyl 2-(4,4-Dimethylthio-3-phenylacetamido-2-azetidinone-1-yl)acetate with Trifluoroacetic Acid. The β-lactam **7a** (0.25 g, 0.61 mmol) was stirred with 1 ml of anisole at 0 °C under nitrogen. Trifluoroacetic acid (6 ml) was added to this suspension. After 10 min the TFA–anisole solution was evaporated under vacuum. Sodium bicarbonate (0.25 g in 5 ml of water) and ethyl acetate (5 ml) were added to the residue. The ethyl acetate layer was discarded and the aqueous layer was washed with another 5-ml portion of ethyl acetate. The separated aqueous layer was acidified to ca. pH 4 with 3 N HCl. The precipitate which formed was collected and dried to give 0.14 g of **11**: mp 148–153 °C dec; NMR (acetone-d_6) δ 2.23 (s, 3 H, SCH_3), 2.30 (s, 3 H, SCH_3), 3.73 (s, 2 H, $C_6H_5CH_2$), ca. 4 (broad, 1 H, HN), 4.06 (d, 2 H, J = 5.5 Hz, $HNCH_2$), 7.37 (s, 5 H, C_6H_5), ca. 7.7 (broad, 2 H, HN and CO_2H); ir (KBr) 1735, 1635 cm^{-1}; MS m/e 336 ($M^+ - H_2O$). Anal. Calcd for $C_{15}H_{18}N_2O_4S_2$: C, 50.83; H, 5.11; H, 7.90. Found: C, 50.86; H, 5.05; N, 7.90.

Rearrangement of Methyl 2-(3-Phenoxyaceamido-4,4-dimethylthio-2-azetidinon-1-yl)acetate (7b) with Hog Pancreas Esterase. Five grams of pancreatin (grade II, Sigma) was stirred for 0.5 h at 0 °C in 25 ml of a 0.1 M NaCl–0.05 M $CaCl_2$ solution. The mixture was centrifuged 10 000*g* and the supernatant liquid was collected. The pH of the supernatant was adjusted to 7.0 using 0.1 N NaOH. To this solution was added 100 mg of **7b**. The mixture was sonicated to ensure complete dispersion. After stirring for 0.5 h at 0 °C, with periodic addition of 0.1 N NaOH to maintain pH at 7.0, the mixture was poured into 300 ml of acetone. The mixture was filtered through Celite and the filter cake was washed thoroughly with acetone. The filtrate was evaporated and the resulting solid was recrystallized from acetone–hexane to afford 70 mg of **12**: mp 135–138 °C; NMR δ 2.33 (s, 6 H, SCH_3), 3.78 (s, 3 H, OCH_3), 4.23 (d, 2 H, J = 5 Hz, HNCH_2), 4.58 (s, 2 H, OCH_2), 7.17 (m, 5 H, C_6H_5), 8.48 (broad singlet, 1 H, NH); ir 1740, 1700, 1665 cm^{-1}; MS m/e 384 (M^+). Calcd for $C_{16}H_{20}N_2O_5S_2$: C, 49.98; H, 5.24; N, 7.29. Found: C, 49.53; H, 5.09; N, 7.05.

***N*-Butyldimethylthioimine (18).** A mixture of *n*-butylamine (3.65 g, 50 mmol), carbon disulfide (3.8 g, 50 mmol), and potassium carbonate (6.9 g, 50 mmol) was stirred in 60 ml of water for 1 h. Methyl iodide (14.2 g, 100 mmol) was added and the mixture was stirred for an additional 3 h, at which time the mixture was extracted with diethyl ether. After drying (Na_2SO_4) and removal of the ether, there was obtained a crude oil. Chromatography of this crude product from ca. 150 g of silica gel with hexane afforded 3.2 g (32%) of the oily dimethylthiomine **18**: NMR δ ca. 1.34 (m, 7 H, $CH_2CH_2CH_3$), 2.35 (s, 3 H, SCH_3), 2.53 (s, 3 H, SCH_3), 3.40 (t, 2 H, J = 6 Hz, NCH_2CH_2); ir (film) 1579 cm^{-1}.

1-Butyl-3-azido-4,4-dimethylthio-2-azetidinone (19). The procedure was similar to that used in the preparation of β-lactams **10a** and **10b**. Using 0.354 g (2 mmol) of the imine **18** and ca. 2 equiv each of triethylamine and azidoacetyl chloride, a 92% yield

of β-lactam **19** was obtained as an oil after silica gel chromatography with hexene–diethyl ether (5:1): NMR δ 0.95 (t, 3 H, J = 6 Hz, CH_2CH_3), 1.52 (m, 4 H, CH_2CH_2), 2.20 (s, 3 H, SCH_3), 2.24 (s, 3 H, SCH_3), 3.21, (t, 2 H, J = 6 Hz, NCH_2CH_2), 4.69 (s, 1 H, N_3CH); ir ($CHCl_3$) 2117, 1763 cm^{-1}; MS m/e 213 ($M^+ - SCH_3$). Anal. Calcd for $C_9H_{16}N_4OS_2$: C, 41.51; H, 6.19; N, 21.52. Found: C, 41.22; H, 6.25; N, 21.22.

Benzhydryl 2-(Dimethylthioimino)-3-methyl-2-butenoate (22). Diphenyldiazomethane (0.5 g, 2.58 mmol) was added to a solution of 0.4 g (1.95 mmol) of acid **21a**[14] in 25 ml of benzene. The solution was heated at reflux for 80 min. Removal of the benzene and chromatography from ca. 40 g of silica gel with hexane–diethyl ether (8:1) afforded 0.623 g (86%) of the ester **21b.** Recrystallization from hexane afforded a solid: mp 99–102 °C; NMR δ 1.16 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 2.51 (s, 3 H, SCH_3), 4.70 (s, 1 H, NCH), 6.96 [s, 1 H, $(C_6H_5)_2CH$], 7.31 (broad singlet, 10 H, C_6H_5); ir ($CHCl_3$) 1745, 1540 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_2S_2$: C, 64.66; H, 5.70; N, 3.77. Found: C, 64.85; H, 5.58; N, 3.42.

The ester **21b** (0.464 g, 1.25 mmol) was dissolved in 5 ml of dry THF. This solution was added dropwise to a THF solution (10 ml) of potassium *tert*-butoxide (0.21 g, 1.88 mmol) at −65 °C. After 30 min, methyl iodide (0.205 g, 1.44 mmol) was added and the solution was warmed to room temperature. Water (ca. 40 ml) was added and the mixture was extracted with diethyl ether. After drying (Na_2SO_4) and removal of ether, 0.425 g (88%) of the oily dimethylthioimine **22** was obtained. A sample crystallized on standing to give a white solid: mp 34–35 °C; NMR δ 1.66 (s, 3 H, SCH_3), 2.11 (s, 3 H, SCH_3), 2.41 (s, 6 H, $=C-CH_3$), 6.87 [s, 1 H, $CH(C_6H_5)_2$], 7.29 (broad singlet, 10 H, C_6H_5); ir ($CHCl_3$) 1708, 1558 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_2S_2$: C, 65.42; H, 6.01; N, 3.63. Found: C, 65.20; H, 6.21; N, 3.56.

Benzhydryl 2-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)-3-methyl-2-butenoate (23). To the imine **22** (0.423 g, 1.1 mmol) in 20 ml of methylene chloride was added 0.132 g of azidoacetyl chloride (1.1 mmol) over ca. 2 min at 5 °C under nitrogen. Triethylamine (0.111 g, 1.1 mmol) was added over 20 min. This order of addition was repeated until a total of 4 equiv of the acid chloride and amine had been added. The mixture was washed with water and dried over Na_2SO_4. The solution was concentrated to a small volume and some polar material was precipitated by the addition of diethyl ether. Filtration and removal of ether afforded a brown gum. This material was dissolved in acetonitrile and applied to a countercurrent distribution device[15] with heptane as the moving phase. In this manner 0.313 g (61%) of β-lactam **23** was obtained as an oil: NMR (C_6D_6) δ 1.60 (s, 3 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 1.78 (s, 3 H), 4.17 (s, 1 H, N_3CH), 7.07 (m, 11 H); ir ($CHCl_3$) 2117, 1771, 1716 cm^{-1}.

Reduction and Acylation of 23. The azide **23** (0.106 g, 0.23 mmol) in 8 ml of methanol was treated with 0.6 ml of a 22% ammonium sulfide solution at room temperature for 5 min. The reaction mixture was diluted with 20 ml of water and extracted with methylene chloride. The methylene chloride solution was dried over Na_2SO_4. The solvent was removed under vacuum and the residue was taken up in 10 ml of methylene chloride. To this solution was added 0.6 ml of triethylamine and 0.11 g (0.64 mmol) of phenoxyacetyl chloride at ca. 0 °C. After 20 min the mixture was washed with water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was dissolved in diethyl ether. Addition of hexane resulted in the precipitation of polar impurities. Removal of solvent under vacuum gave **25** as an oil (ca. 85% purity): NMR δ 1.79 (s, 3 H), 2.01 (s, 3 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 4.56 (s, 2 H, OCH_2), 5.48 (d, 1 H, J = 9 Hz, HNCH), ca. 7.2 (m, 11 H); ir ($CHCl_3$) 1775, 1695 cm^{-1}.

Rearrangement of 25. A small sample (ca. 15 mg) of **25** was stirred with ca. 0.2 g of silica gel in 5 ml of diethyl ether for 3 h. The mixture was filtered and washed with ether. Removal of the ether and chromatography of the residue on a 20 × 20 cm, 0.5 mm silica gel GF plate afforded 7.5 mg of an oil whose spectral properties were consistent with **26.** Crystallization from acetone–hexane afforded a white solid: mp 174–176 °C; NMR δ 2.02 (s, 3 H), 2.07 (s, 3 H), 2.10 (s, 3 H), 2.28 (s, 3 H), 4.48 (s, 2 H, OCH_2), ca. 7.3 (m, 11 H), 7.78 (broad singlet, 1 H, HN), 8.55 (broad singlet, 1 H, HN); ir 1705, 1685 cm^{-1}; MS m/e 409 [$M^+ - (C_6H_5)_2CH$]. Anal. Calcd for $C_{31}H_{32}N_2O_5S_2$: C, 64.56; H, 5.59; N, 4.86. Found: C, 64.43; H, 5.72; N, 4.64.

Hydrolysis of 7b. The lactam **7b** (35 mg, 0.091 mmol) was dissolved in 1 ml of methanol. To this solution was added 0.96 ml of 0.1 M aqueous lithium hydroxide and the mixture was stirred at room temperature until TLC analysis indicated virtually complete disappearance of **7b.** Water (5 ml) was added and the mixture was acidified with HCl. The mixture was extracted thoroughly with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and concentrated to a foam. Treatment of this solid with acetone–hexane gave 15 mg of **6b** as a white solid, mp 121–123 °C. A total of 9 mg of the starting ester **7b** was recovered from the acetone–hexane solution: NMR δ 2.03 (s, 3 H, SCH_3), 2.15 (s, 3 H, SCH_3), 4.01 (s, 2 H, NCH_2), 4.6 (s, 2 H, OCH_2), 5.69 (d, 1 H, J = 10 Hz, HNCH), 6.6 (s, 1 H, CO_2H), 6.9–7.5 (m, 5 H, C_6H_5), 7.74 (d, 1 H, J = 10 Hz, NH); ir ($CHCl_3$) 1765, 1720 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_5S_2$: C, 48.63; H, 4.90; N, 7.56. Found: C, 48.87; H, 5.12; N, 7.30.

The hydrolysis of **7b** was repeated using 391 mg of **7b.** The resulting acid was taken up in ca. 1 ml of ethyl acetate and this solution was added to ca. 3 ml of a saturated solution of sodium 2-ethylhexanoate in isopropyl alcohol. Addition of ca. 3 ml of diethyl ether gave a precipitate which was collected by filtration and was washed with additional diethyl ether. In this manner 60 mg of **29** was obtained as a light yellow, hydroscopic solid. NMR analysis indicated a purity of ca. 90%.

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Registry No.—**6b,** 58091-02-4; **7a,** 58091-03-5; **7b,** 58091-04-6; **8a,** 58091-05-7; **8b,** 58091-06-8; **9a,** 58091-07-9; **9b,** 58091-08-0; **10a,** 58091-09-1; **10b,** 58091-10-4; **11,** 58091-11-5; **12,** 58091-12-6; **14,** 58091-13-7; **15,** 58091-14-8; **16a** isomer 1, 58091-15-9; **16a** isomer 2, 58091-16-0; **16b** isomer 1, 58091-17-1; **16b** isomer 2, 58091-18-2; **17,** 58091-19-3; **18,** 54208-96-7; **19,** 58091-20-6; **21a,** 58091-21-7; **21b,** 58091-22-8; **22,** 58091-23-9; **23,** 58091-24-0; **25,** 58091-25-1; **26,** 58091-26-2; **27,** 58091-27-3; *tert*-butyl aminoacetate, 6456-74-2; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; methyl glycinate hydrochloride, 5680-79-5; azidoacetyl chloride, 30426-58-5; L-valine hydrochloride methyl ester, 6306-52-1; phenylacetyl chloride, 103-80-0; phenoxyacetyl chloride, 701-99-5; glycine, 56-40-6; formic–acetic anhydride, 2258-42-6; *N*-formylglycine, 2491-15-8; methyl *N*-formylglycinate, 3152-54-9; phosphorus pentasulfide, 1314-80-3; methyl *N*-thioformylglycinate, 58091-28-4; *syn*-methyl 2-(methylthioimino)acetate, 58091-29-5; *anti*-methyl 2-(methylthioimino)acetate, 58091-30-8; methyl 2-(*trans*-3′-phenylacetamido-4′-methylthio-2′-azetidinon-1′-yl)acetate, 58091-31-9; trifluoroacetic acid, 76-05-1; hog pancreas esterase, 9001-08-5; *n*-butylamine, 109-73-9; diphenyldiazomethane, 883-40-9.

References and Notes

(1) Contribution No. 462 from the Syntex Institute of Organic Chemistry and No. 2 in the series Studies in β-Lactams.
(2) Syntex Postdoctoral Fellow: (a) 1974–1975; (b) 1973–1974.
(3) For a recent review of β-lactam synthesis see A. K. Mukerjee and R. C. Srivastava, *Synthesis,* 327 (1973).
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A New Synthetic Method for Condensed Heterocycles, Carbazoles, Indoles, and Benzothiophenes, Based on Acid-Catalyzed Cyclization of β-Keto Sulfoxides[1]

Yuji Oikawa and Osamu Yonemitsu*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

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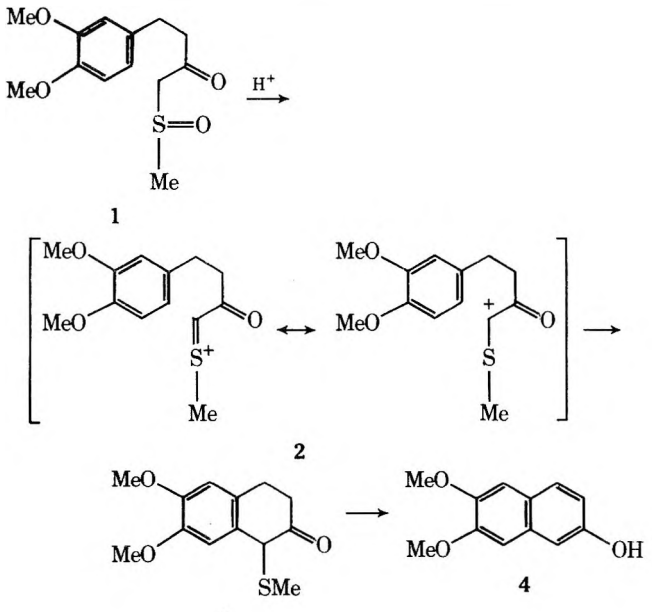
On heating with trichloroacetic acid or trifluoroacetic acid, β-keto sulfoxides (**5–11**) derived from indolepropionic acid, indolebutyric acids, and tryptophan cyclized to 1-methyl-2-oxotetrahydrocarbazoles (**12–18**). This cyclization proceeded more smoothly upon treatment with toluenesulfonic acid in tetrahydrofuran. Treatment with this acid in acetonitrile gave aromatized 2-hydroxycarbazoles (**20, 21, 26**). In the presence of methanol and ethanol, methoxy (**24, 27**) and ethoxy compounds (**25**) were isolated. The tryptophan derivative (**8**) gave an oxazolocarbazole (**28**). β-Keto sulfoxides (**31, 32**) with carboxamides introduced before the cyclization gave tetracyclic compounds (**35, 36**), as well as the expected products. The isolation of **35** and **36** clearly indicates the presence of intermediary indolenines (**38, 39**). Similarly, pyrrole derivatives (**40, 41**) gave unaromatized and aromatized indole derivatives (**42–45**). Thiophene derivatives (**46–48, 56**) also gave benzothiophenes (**49–53, 55, 57**), though somewhat inefficiently.

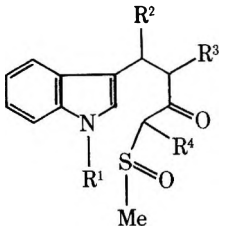
Recently we described an extended application of the Pummerer reaction for a new synthesis of condensed aromatics such as naphthalene and phenanthrene derivatives through the acid-catalyzed cyclization of β-keto sulfoxides (e.g., **1** → **3, 4**).[2] A common and key step in this cyclization is the intramolecular nucleophilic attack of aromatic ring on the carbocations (**2**) derived from β-keto sulfoxides (**1**) in the presence of acids. Accordingly, the use of electron-rich heterocycles instead of aromatics as intramolecular nucleophiles may give condensed heterocycles.



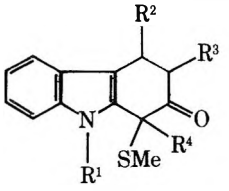
There are many useful synthetic methods for the preparation of condensed heterocycles, the majority of which naturally involves the procedures of the construction of heterocyclic rings.[3] In the present paper we report a new synthetic method for condensed heterocycles constructing the benzene ring from β-keto sulfoxides.

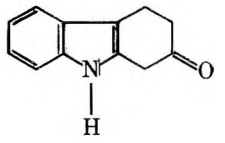
Carbazoles. Since indole is the most typical electron-rich heterocycle, synthesis of carbazoles through the cyclization of β-keto sulfoxides having an indole ring as nucleophiles was first examined (Table I).

Treatment of **5**, prepared from methyl indolepropionate and sodium methylsulfinylmethide,[4] with a half-molar quantity of trichloroacetic acid in boiling dichloroethane for 1 h resulted in its ready conversion to 1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (**12**) in a fair yield. Cyclization with trichloroacetic acid also proceeded smoothly in benzene, but not in tetrahydrofuran. The composition of **12** was determined by mass spectrometry and elemental analysis as $C_{13}H_{13}NOS$. In its ir spectrum, NH and CO groups appear at 3280 and 1690 cm^{-1}, respectively, and its NMR spectrum has distinct signals at 2.20 (SCH_3) and 4.36 ppm (COCHSMe), and no signal assignable to the proton at the C-2 position in the indole ring.



5, $R^1 = R^2 = R^3 = R^4 = H$
6, R^1 = Me; $R^2 = R^3 = R^4 = H$
7, $R^1 = CH_2C_6H_5$; $R^2 = R^3 = R^4 = H$
8, R^1 = Me; $R^2 = R^4 = H$; R^3 = NHAc
9, $R^1 = R^2 = R^3 = H$; R^4 = Me
10, $R^1 = R^2 = R^4 = H$; R^3 = Me
11, $R^1 = CH_2C_6H_5$; R^2 = Me; $R^3 = R^4 = H$





12, $R^1 = R^2 = R^3 = R^4 = H$
13, R^1 = Me; $R^2 = R^3 = R^4 = H$
14, $R^1 = CH_2C_6H_5$; $R^2 = R^3 = R^4 = H$
15, R^1 = Me; $R^2 = R^4 = H$; R^3 = NHAc
16, $R^1 = R^2 = R^3 = H$; R^4 = Me
17, $R^1 = R^2 = R^4 = H$; R^3 = Me
18, $R^1 = CH_2C_6H_5$; R^2 = Me; $R^3 = R^4 = H$

19

N-Methyl (**6**) and *N*-benzyl compounds (**7**) also gave the corresponding cyclization products, **13** and **14**, by treatment with either trichloroacetic acid or trifluoroacetic acid. The cyclization of **6** and **7** proceeded more smoothly in boiling tetrahydrofuran in the presence of a stronger acid, *p*-toluenesulfonic acid (2 equiv), though the acid usually facilitates the formation of aromatized products (vide infra). Compound **8** drived from tryptophan easily gave **15**.

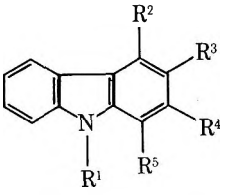
Table I. Cyclization of β-Keto Sulfoxides to 1-Methylthio-2-oxo-1,2,3,4-tetrahydrocarbazoles

Compd	Acid	Solvent	Temp	Product	Yield, %
5	CCl_3CO_2H	$(CH_2Cl)_2$	Reflux	12	68
6	CCl_3CO_2H	Benzene	Reflux	13	60
6	CF_3CO_2H	Benzene	Reflux	13	74
6	TsOH	THF	Reflux	13	82
7	TsOH	THF	Reflux	14	75
8	CF_3CO_2H	Benzene	Reflux	15	66
9	CCl_3CO_2H	$(CH_2Cl)_2$	Reflux	16	10.7
10	CCl_3CO_2H	$(CH_2Cl)_2$	Reflux	17	45
11	TsOH	THF	Reflux	18	42

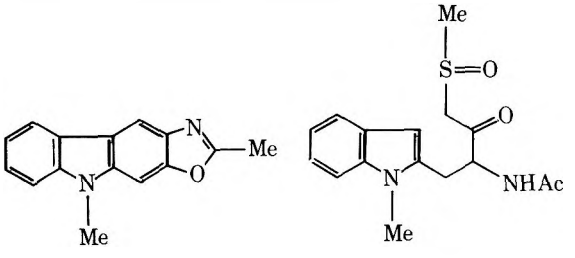
Similarly, **10** and **11** derived from indolebutyrates gave **17** and **18**, respectively.

1-Methylthio-2-oxo-1,2,3,4-tetrahydrocarbazoles were easily converted to 2-oxo-1,2,3,4-tetrahydrocarbazoles by reductive desulfurization. As a typical example, **12** was reduced with aluminum amalgam to give **19** in a high yield.[5] This may provide a general and practical method for the preparation of 2-tetralone-type compounds.[6]

On treatment with toluenesulfonic acid in boiling acetonitrile, **5** gave 2-hydroxycarbazole (**20**) (Table II). Under these conditions, **12** also aromatized to **20** with concomitant elimination of methanethiol. Similarly **6** gave **21**, but at 50 °C a 2-methylthio compound (**22**) as well as **21** was isolated. Compound **22** was easily converted to *N*-methylcarbazole (**23**) by treatment with Raney Ni. The yields of **20** and **21** were somewhat improved by the use of dioxane instead of acetonitrile. In the presence of methanol and ethanol, **6** gave methoxy (**24**) and ethoxy compounds (**25**), respectively. Compound **10** in acetonitrile gave 2-hydroxy-3-methylcarbazole (**26**).[8] In the presence of methanol, **11** gave **27**. Compound **8** in the absence of alcohol gave recyclized oxazolocarbazole (**28**), and not a phenolic compound. Acid-catalyzed cyclization of 2-acylaminophenols is known to be the most common way for the synthesis of benzoxazoles.[9] Compound **28** has a characteristic uv spectrum, and no signal assignable to an amide group in its ir spectrum. Compound **29** derived from isotryptophan similarly gave an isomeric oxazolocarbazole (**30**), determined by mass spectrometry, though in a very poor yield because of instability of **29** to acids.



20, $R^1 = R^2 = R^3 = R^5 = H$; $R^4 = OH$
21, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = OH$
22, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = SMe$
23, $R^1 = Me$; $R^2 = R^3 = R^4 = R^5 = H$
24, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = OMe$
25, $R^1 = Me$; $R^2 = R^3 = R^5 = H$; $R^4 = OEt$
26, $R^1 = R^2 = R^5 = H$; $R^3 = Me$; $R^4 = OH$
27, $R^1 = CH_2C_6H_5$; $R^2 = Me$; $R^3 = R^5 = H$; $R^4 = OMe$



28 **29**

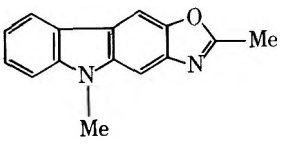


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Table II. Carbazoles from β-Keto Sulfoxides

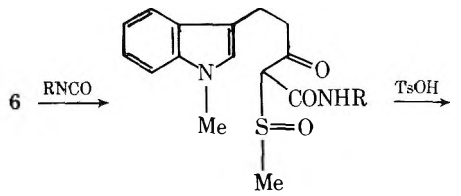
Compd	Acid	Solvent	Temp	Product	Yield, %
5	TsOH	MeCN	Reflux	20	40
5	TsOH	Dioxane	Reflux	20	55
6	TsOH	MeCN	50 °C	21	34
				22	22
6	TsOH	Dioxane	Reflux	21	54
6	TsOH	Me_2CO–MeOH	Reflux	24	47
6	TsOH	Me_2CO–EtOH	Reflux	25	40
8	TsOH	Benzene	Reflux	28	60
8	TsOH	MeCN	Reflux	28	80
10	TsOH	MeCN	Reflux	26	50
11	TsOH	Me_2CO–MeOH	Reflux	27	23
29	TsOH	MeCN	Reflux	30	3

As previously described,[2a] the formation of aromatized products consists of a series of two acid-catalyzed reactions, the cyclization of β-keto sulfoxides and the aromatization with loss of methanethiol. The latter usually requires a stronger acid and/or a higher temperature. In the case of **6**, the reaction with toluenesulfonic acid in tetrahydrofuran (bp 66 °C) gave the cyclization product (**13**) in a high yield, while in dioxane (bp 101 °C) only aromatized product (**21**) was formed. Thus the two types of products are arbitrarily available. This is one of the principal advantages of the synthetic method presented here, though the selection of the proper acid and solvent, especially the latter, is quite important.

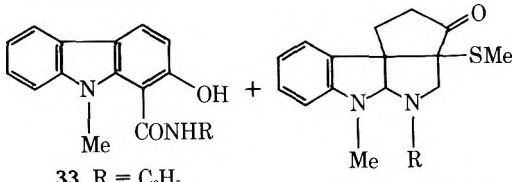
A substituent can be introduced before the acid-catalyzed cyclization at the methylene group between the carbonyl and sulfoxide groups of β-keto sulfoxides because of the high reactivity for electrophiles. The potassium salt prepared from **5** with potassium hydride in tetrahydrofuran was allowed to react with methyl iodide, and a methylated compound (**9**) was isolated in 78% yield. On treatment with trichloroacetic acid, **9** gave a cyclization product (**16**), though in a poor yield.

The sodium salt of **6** in tetrahydrofuran reacted with phenyl isocyanate and ethyl isocyanate to give **31** (94%) and **32** (97%), respectively. On treatment with toluenesulfonic acid in acetonitrile, **31** interestingly gave mainly a tetracyclic compound (**35**, 45%) as well as an expected product (**33**, 30%). The structure assignment of **35** rests on its spectral data. In its ir spectrum, **35** has two carbonyl groups assignable to a five-membered ketone (1745 cm^{-1}) and a five-membered lactam (1690 cm^{-1}). Distinct signals in its NMR spectrum appear at 2.28 (SCH_3), 2.60 (NCH_3), and 5.40 ppm (NCHN), and its uv spectrum is characteristic of indoline derivatives. Similarly, **32** gave **34** and **36** in 41 and 33% yield, respectively. Under milder conditions, viz., on treatment with toluenesulfonic acid at 50 °C in dioxane, **32** gave **36** (40%) and **37** (44%). In analogy with **35**, the structure of **36** was determined from spectral data, and, especially in the NMR spectrum, three singlet signals at 2.04 (3 H), 3.06 (3 H), and 4.88 ppm (1 H) are clearly assigned.

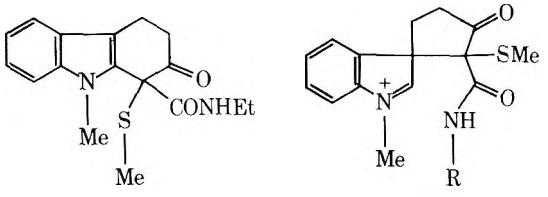
It is well known that the formation of 2,3-disubstituted indoles from 3-substituted indoles by electrophilic alkylation usually involves the initial formation of 3,3-disubstituted indolenines, followed by the rearrangement of one



31, R = C_6H_5
32, R = Et



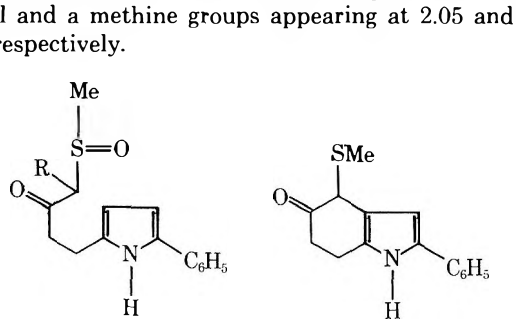
33, R = C_6H_5
34, R = Et
35, R = C_6H_5
36, R = Et



37
38, R = C_6H_5
39, R = Et

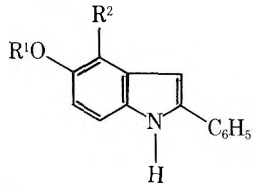
substituent from C-3 to C-2, rather than the direct alkylation at C-2.[10] This mechanism also acts in the cyclization of β-keto sulfoxides, because **35** and **36** can be formed through indolenines **38** and **39**, respectively. The isolation of **35** and **36** may provide an additional example proving the presence of intermediary indolenines in the electrophilic substitution of 3-substituted indoles by the direct trapping.

Indoles. The cyclization of pyrrole derivatives to indoles was examined next. The easily synthesized ethyl 5-phenylpyrrole-2-propionate[11] was converted to a β-keto sulfoxide (**40**), which was heated under reflux in tetrahydrofuran in the presence of 0.4 molar equiv of toluenesulfonic acid to give a cyclization product (**42**) (Table III). The structure was easily determined from its spectral data, especially by the characteristic signals in its NMR spectrum of an *S*-methyl and a methine groups appearing at 2.05 and 4.04 ppm, respectively.



40, R = H
41, R = $CONHC_6H_5$

42



43, R^1 = Me; R^2 = H
44, R^1 = Et; R^2 = H
45, R^1 = H; R^2 = $CONHC_6H_5$

When **40** was heated in methanol with an equimolar amount of toluenesulfonic acid, 5-methoxy-2-phenylindole (**43**) was isolated in 80% yield. Similarly in ethanol, **40** gave an ethoxy compound (**44**). Compound **41** derived from **40** with phenyl isocyanate was heated with toluenesulfonic acid in 2-propanol to give 4-substituted indole derivative (**45**) in 91% yield. The reaction also proceeded, though inefficiently, either in acetonitrile or in benzene.

Table III. Cyclization of β-Keto Sulfoxides to Indole Derivatives

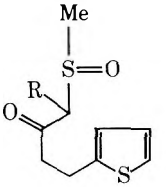
Compd	Acid	Solvent	Temp	Product	Yield, %
40	TsOH	THF	Reflux	**42**	63
40	TsOH	MeOH	Reflux	**43**	80
40	TsOH	EtOH	Reflux	**44**	72
41	TsOH	*i*-PrOH	Reflux	**45**	91

Table IV. Cyclization of β-Keto Sulfoxides to Benzothiophenes

Compd	Acid	Solvent	Temp	Product	Yield, %
46	CF_3CO_2H	Benzene	Reflux	**49**	50
46	TsOH	MeCN	Reflux	**50**	56
				51	14
				54	7
46	TsOH	MeOH	Reflux	**52**	14
				54	5
46	CCl_3-CO_2H	MeCN–MeOH	Reflux	**52**	22
47	TsOH	Benzene	Reflux	**53**	55
48	TsOH	Benzene	Reflux	**55**	25
56	TsOH	MeCN	Reflux	**57**	53

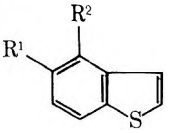
Benzothiophenes. β-Keto sulfoxides having a thiophene ring were also subjected to the acid-catalyzed reaction and formed benzothiophene derivatives (Table IV). Thiophene is known to be somewhat less reactive than pyrrole and indole toward the usual electrophilic reagents, and this was also found to be the case in the cyclization of β-keto sulfoxides.

Compound **46** prepared from methyl thiophene-2-propionate was heated with trifluoroacetic acid in benzene to give a cyclization product (**49**), which has distinct signals of *m/e* 198 (M^+), and 2.05 (SCH_3) and 4.02 ppm ($COCHSCH_3$) in the mass and NMR spectra. In aromatization conditions with toluenesulfonic acid in acetonitrile, **46** gave 5-hydroxybenzothiophene (**50**) with unavoidable concomitant formation of 5-methylthiobenzothiophene (**51**) and a thioacetal (**54**).[12] In methanol, **46** gave a methoxy compound (**52**) also accompanied with **51**, but the treatment with a large excess of trichloroacetic acid in a mixture

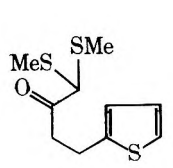


46, R = H
47, R = $CONHC_6H_5$
48, R = CH_2CO_2Me

49



50, R^1 = OH; R^2 = H
51, R^1 = SMe; R^2 = H
52, R^1 = OMe; R^2 = H
53, R^1 = OH; R^2 = $CONHC_6H_5$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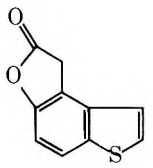
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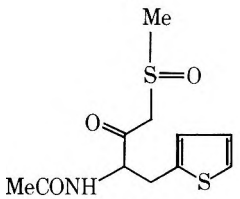
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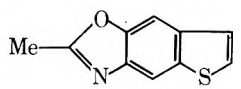
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of methanol and acetonitrile gave only **52** though in a poor yield. On treatment with toluenesulfonic acid, **47** prepared from **46** and phenyl isocyanate gave a 4-substituted benzothiophene (**53**), and similarly **48** prepared from **46** and methyl bromoacetate gave a lactone (**55**). In analogy with **8** and **29**, compound **56** derived from thiophene-2-alanine gave an oxazolobenzothiophene (**57**), which has the composition of $C_{10}H_7NOS$ as determined by the mass spectrum and elemental analysis, and neither a phenol nor amide in its ir spectrum.

Concluding Remarks. Although many useful methods are available for the synthesis of condensed heteroaromatics, the potential utility of the acid-catalyzed cyclization of β-keto sulfoxides in the area of heterocyclic chemistry can be emphasized because of the following advantages and characteristics. (1) The majority of usual synthetic methods for condensed heteroaromatics such as indole and benzothiophene involves the preparation of a heterocyclic ring moiety through ring closure, while the method described in this paper is characterized by the construction of a benzene ring. (2) The starting materials, β-keto sulfoxides, are easily prepared by the well-known reaction of methylsulfinyl carbanion[4] with the corresponding esters. (3) Two types of compounds, unaromatized cyclic β-keto sulfides and aromatized compounds, are arbitrarily obtained by the selection of reaction conditions. (4) Some substituents can be introduced in a benzene ring by the prior introduction of substituents at the methylene group between sulfinyl and carbonyl groups of β-keto sulfoxides.

Experimental Section

2-(3-Indolyl)ethyl Methylsulfinylmethyl Ketone (5). The anion of Me_2SO was prepared according to the procedure by Corey[4] from 1.08 g of NaH, 25 ml of Me_2SO, and 20 ml of THF. To this solution 3.0 g of methyl indole-3-propionate[13] dissolved in 10 ml of THF was added dropwise at 0–5 °C. After being stirred for an additional 1 h at room temperature, the mixture was poured into ice–water, acidified with HCl to pH 4–5, and then extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent left an oil, which was crystallized from EtOAc to give a colorless powder in 75% yield: mp 97–99° (from EtOAc); ν (Nujol) 3350, 1710 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.50; H, 6.17; N, 5.55.

2-(1-Methyl-3-indolyl)ethyl Methylsulfinylmethyl Ketone (6). Compound **6** was synthesized from methyl (1-methyl-3-indolyl)propionate[14] and Me_2SO in 77% yield: mp 82–83 °C; ν (Nujol) 1695 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32; S, 12.17. Found: C, 64.03; H, 6.48; N, 5.10; S, 11.94.

2-(1-Benzyl-3-indolyl)ethyl Methylsulfinylmethyl Ketone (7). To a stirring suspension of 2.4 g of NaH in 75 ml of Me_2SO was added dropwise 20.3 g of methyl indole-3-propionate[13] in 25 ml of THF keeping the temperature below 20 °C by occasional cooling. After the evolution of hydrogen ceased, the mixture was cooled in an ice bath and 12.7 g of benzyl chloride in 10 ml of THF was added dropwise. The stirring was continued for 2 h at room temperature. The reaction mixture was poured into 300 ml of saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was distilled under reduced pressure to give 23 g (80%) of methyl 3-(1-benzyl-3-indolyl)propionate: bp 205–207 °C (2 mm); *m/e* 293 (M^+), 220, 91 (base peak).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.78; H, 6.48; N, 4.87.

This ester was converted to compound **7** in 88% yield: mp 90–93° (from EtOAc); ν (Nujol) 1710 cm^{-1}.

Anal. Calcd for $C_{20}H_{21}NO_2S$: C, 70.78; H, 6.24; N, 4.13; S, 9.43. Found: C, 70.61; H, 6.09; N, 4.25; S, 9.18.

1-Acetamido-2-(1-methyl-3-indolyl)ethyl Methylsulfinylmethyl Ketone (8). *N*-Acetyl-*dl*-tryptophan methyl ester[15] was methylated with methyl iodide in a manner similar to the benzylation described above to give methyl 2-acetamido-3-(1-methyl-3-indolyl)propionate in 97% yield as an oil: ν (neat) 3280, 1735, 1650 cm^{-1}; *m/e* 274 (M^+), 144 (base peak).

This ester was converted to compound **8** in 79% yield: mp 128–131 °C (from EtOAc); ν (Nujol) 3350, 1705, 1638 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.99; H, 6.29; N, 8.75; S, 9.98. Found: C, 59.85; H, 6.33; N, 8.65; S, 9.97.

2-(3-Indolyl)ethyl 1-Methylsulfinylethyl Ketone (9). To an ice-cooled solution of the K salt of **5**, prepared from 0.249 g of **5** and 40 mg of KH in 11 ml of THF, 0.150 g of methyl iodide was added in one portion with stirring. The stirring was continued for 3 h at room temperature, and then the mixture was poured into 30 ml of saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated to leave an oil, which was purified by passing in CH_2Cl_2–EtOAc (1:1) through silica gel to give 0.205 g (78%) of **9** (oil) as a diastereomeric mixture: ν (neat) 3400, 3250, 1700, 1030 cm^{-1}; *m/e* 263 (M^+), 200, 144, 130 (base peak); δ ($CDCl_3$) 1.26 (d, 2 H, J = 8 Hz), 1.34 (d, 1 H, J = 8 Hz), 2.36 (s, 3 H), 2.84–3.14 (m, 4 H), 3.72 (broad q, 1 H), 6.7–7.6 (m, 5 H), 8.44 (broad s, 1 H).

1-(3-Indolylmethyl)ethyl Methylsulfinylmethyl Ketone (10). Compound **10** was synthesized from ethyl 3-(3-indolyl)-2-methylpropionate[16] and Me_2SO in 97% yield as an oil (1:1.3 diastereomeric mixture): ν (neat) 3325, 1710, 1040 cm^{-1}; *m/e* 247 (M^+), 130 (base peak); δ ($CDCl_3$) 1.20 (broad d, 3 H, J = 6 Hz), 2.40 (s, 1.3 H), 2.50 (s, 1.7 H), 2.70–3.30 (m, 3 H), 3.62 (0.9 H), 3.67 (1.1 H), 6.9–7.7 (m, 5 H), 8.50 (broad s, 1 H).

Ethyl 3-(1-Benzyl-3-indolyl)butyrate. A solution of 85 g of *N*-(3-indolyl-1-ethyl)-*N*-isopropylamine[17a] and 89.9 g of diethyl malonate in 450 ml of DMF was heated under reflux for 7.5 h. After evaporation of the solvent, the residue was dissolved in ether. The solution was washed with H_2O, 5% HCl, and H_2O, dried and then concentrated to leave crude diethyl 1-(3-indolyl)ethylmalonate. The crude ester was dissolved in a solution of 40 g of NaOH in 200 ml of EtOH and 84 ml of H_2O, and heated under reflux for 2 h. The reaction mixture was concentrated to remove the EtOH, diluted with H_2O, acidified with HCl, and then extracted with ether. The extract was washed with H_2O, dried, and evaporated to leave 1-(3-indolyl)ethylmalonic acid as an oil. The acid was dissolved in 100 ml of pyridine and heated under reflux for 5.5 h. After evaporation of the pyridine, to the residue was added H_2O, and the mixture was acidified with HCl to pH 3 and extracted with EtOAc. The extract was dried and evaporated to leave 3-(3-indolyl)butyric acid,[17b] which was esterified in the usual manner to yield 25.7 g (overall yield 26.5%) of ethyl 3-(3-indolyl)butyrate. The ester was benzylated as described above to give 27.5 g (73%) of ethyl 3-(1-benzyl-3-indolyl)butyrate: bp 197–200° (1 mm); *m/e* 321 (M^+), 234, 91 (base peak).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.62; H, 7.27; N, 4.45.

2-(1-Benzyl-3-indolyl)propyl Methylsulfinylmethyl Ketone (11). Compound **11** was synthesized from ethyl 3-(1-benzyl-3-indolyl)butyrate in 97% yield as an oil (1:1.3 diastereomeric mixture): ν (neat) 1710, 1041 cm^{-1}; δ ($CDCl_3$) 1.40 (d, 1.3 H, J = 6 Hz), 1.42 (d, 1.7 H, J = 6 Hz), 2.43 (s, 1.3 H), 2.50 (s, 1.7 H), 2.55–3.10 (m, 3 H), 3.62 (2 H), 6.9–7.4 (m, 9 H), 7.5–7.8 (m, 1 H).

1-Acetamido-2-(1-methyl-2-indolyl)ethyl Methylsulfinylmethyl Ketone (29). Ethyl 2-acetamido-3-(2-indolyl)propionate[18] was methylated as described above to yield ethyl 2-acetamido-3-(1-methyl-2-indolyl)propionate in 87% yield as an oil: ν (neat) 3350, 3300, 1740, 1660 cm^{-1}.

This ester was converted to **29** in 55% yield as a hard oil of a diastereomeric mixture: ν 3250, 1720, 1660, 1020 cm^{-1}; δ ($CDCl_3$) 1.96 (s, 3 H), 2.62 (s, 1.5 H), 2.65 (s, 1.5 H), 3.65 (s, 3 H), 3.3–3.8 (m, 5 H), 6.32 (s, 1 H), 7.17–7.30 (4 H).

1-Methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (12). A solution of 0.63 g of **5** and 0.126 g of CCl_3CO_2H in 30 ml of $(CH_2Cl)_2$ was heated under reflux for 2.5 h. After being cooled, the solution was washed with $NaHCO_3$ solution, dried, and evaporated to leave a solid, which was recrystallized from EtOH to give 0.397 g (68%) of **12:** mp 149–151°; ν (Nujol) 3280, 1690 cm^{-1}; *m/e* 231 (M^+), 184 (base peak), 156; δ ($CDCl_3$) 2.20 (s, 3 H), 2.6–3.4 (m, 4 H), 4.36 (s, 1 H), 7.1–7.6 (m, 4 H), 8.13 (broad s, 1 H).

Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.52; H, 5.67; N, 6.06; S, 13.84. Found: C, 67.33; H, 5.68; N, 5.99; S, 13.71.

9-Methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (13). A. A solution of 0.132 g of **6** and 0.19 g of $TsOH-H_2O$ in 6 ml of THF was heated under reflux for 2 h. After being cooled, the solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove THF, and extracted with $CHCl_3$. The extract was dried and evaporated to leave crude **13,** which was purified by passing in $CHCl_3$ solution through a silica gel column to give 0.101 g (82%) of **13.** Recrystallization from EtOH gave colorless scales: mp 147–148 °C; ν (Nujol) 1705 cm^{-1}; λ (EtOH) 288 nm; δ ($CDCl_3$) 2.19 (s, 3 H), 2.5–3.5 (4 H), 3.73 (s, 3 H), 4.15 (s, 1 H), 7.0–7.52 (4 H); *m/e* 245 (M^+), 198 (base peak).

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.55; H, 6.16; N, 5.71; S, 13.04. Found: C, 68.39; H, 6.09; N, 5.59; S, 13.02.

B. The above neutralized reaction mixture was concentrated to remove the THF and allowed to stand at room temperature. The precipitated crystals were collected by filtration and recrystallized from EtOH to give **13** as colorless scales.

9-Benzyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (14). A solution of 7 (0.339 g) and 0.38 g of $TsOH-H_2O$ in 10 ml of THF was heated under reflux for 3 h. Work-up as described above gave crude **14,** which was purified by passing its CH_2Cl_2–hexane (1:1) solution through silica gel to give 0.24 g (75%) of **14** as an oil. The oil crystallized when its EtOH solution was scratched. Recrystallization from EtOH gave colorless needles: mp 132–133 °C; ν (Nujol) 1700 cm^{-1}; *m/e* 321 (M^+); δ ($CDCl_3$) 2.10 (s, 3 H), 2.4–3.6 (m, 4 H), 3.96 (s, 1 H), 5.46 (2 H), 6.95–7.6 (9 H).

Anal. Calcd for $C_{20}H_{19}NOS$: C, 74.74; H, 5.96; N, 4.36; S, 9.96. Found: C, 74.61; H, 5.93; N, 4.18; S, 9.79.

3-Acetamido-9-methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (15). A solution of 0.16 g of 8 and 0.114 g of CF_3CO_2H in 8 ml of benzene was heated under reflux for 1 h. After being cooled, the solution was washed with $NaHCO_3$ solution, dried, and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with benzene–EtOAc (6:1) gave 0.1 g (66%) of **15** as a solid. Recrystallization from EtOH gave colorless needles: mp 162 °C (sintered from 150 °C); ν (Nujol) 3280, 3080, 1720, 1670, 1650 cm^{-1}; *m/e* 302 (M^+); δ ($CDCl_3$) 2.10 (s, 3 H), 2.16 (s, 3 H), 2.44–2.7 (1 H), 3.70 (s, 3 H), 3.75–4.02 (1 H), 4.32 (s, 1 H), 5.4–5.65 (1 H), 6.60 (broad s, 1 H).

Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.56; H, 6.00; N, 9.27; S, 10.58. Found: C, 63.50; H, 5.98; N, 9.32; S, 10.32.

1-Methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (16). A solution of 0.15 g of **9** and 30 mg of CCl_3CO_2H in 7 ml of $(CH_2Cl)_2$ was heated under reflux for 2 h. The solution was cooled, washed with $NaHCO_3$ solution, and dried. After evaporation of the solvent, the residual oil was chromatographed on a silica gel column. Elution with hexane–CH_2Cl_2 (1:1) gave 15 mg (10.7%) of **16** as an colorless oil: ν (neat) 3350, 1700 cm^{-1}; δ ($CDCl_3$) 1.76 (s, 3 H), 2.00 (s, 3 H), 2.6–3.4 (m, 4 H), 7.1–7.5 (m, 4 H), 8.08 (broad s, 1 H); *m/e* 245 (M^+), 198 (base peak).

3-Methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (17). A solution of 0.263 g of **10** and 0.05 g of CCl_3CO_2H in 12 ml of $(CH_2Cl)_2$ was heated under reflux for 2 h. Work-up as described above gave 0.112 g (45%) of **17:** mp 121–124 °C (from EtOH); ν (Nujol) 3350, 1685 cm^{-1}; *m/e* 245 (M^+), 198 (base peak), 170; δ ($CDCl_3$) 1.29 (d, 3 H, J = 6 Hz), 2.16 (s, 3 H), 2.44–2.74 (m, 1 H), 3.14–3.54 (m, 2 H), 4.28 (d, 1 H, J = 2 Hz).

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.55; H, 6.16; N, 5.71; S, 13.05. Found: C, 68.49; H, 6.14; N, 5.57; S, 13.04.

9-Benzyl-4-methyl-1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (18). A solution of 0.353 g of 11 and 0.13 g of $TsOH-H_2O$ in 8 ml of THF was heated under reflux for 3 h. Work-up as described above gave 0.14 g (42%) of an oil of 18 as a diastereomeric mixture (1:1.5): ν (neat) 1710 cm^{-1}; δ ($CDCl_3$) 1.30 (d, 1.8 H, J = 6 Hz), 1.48 (d, 1.2 H, J = 6 Hz), 2.12 (s, 3 H), 2.2–3.7 (m, 3 H), 3.92 (s, 1 H), 5.44 (2 H), 6.9–7.7 (m, 9 H); *m/e* 335 (M^+), 288, 91 (base peak).

2-Oxo-1,2,3,4-tetrahydrocarbazole (19). To a solution of 0.2 g of **12** in 14 ml of THF and 13 ml of H_2O was added Al amalgam freshly prepared from 0.25 g of Al.[4] The mixture was stirred at 5 °C for 10 min and at room temperature for 30 min, and then filtered to remove the Al amalgam. The filtrate was concentrated and extracted with Et_2O. The extract was dried and evaporated to leave an oil, which was solidified to 0.135 g (95%) of **19:**[5] mp 128–130 °C (from 33% EtOH); ν (Nujol) 3380, 1720 cm^{-1}; *m/e* 185 (M^+), 156, 143 (base peak); δ ($CDCl_3$) 2.6–3.1 (4 H), 3.58 (s, 2 H), 7.0–7.55 (m, 4 H), 7.8 (broad s, 1 H).

2-Hydroxycarbazole (20). A. Compound **5** (0.25 g) was heated under reflux for 1 h with 0.17 g of $TsOH-H_2O$ in 12 ml of MeCN. The solvent was removed in vacuo and the residue was dissolved in Et_2O. The solution was washed with $NaHCO_3$ solution and then extracted with 10% NaOH. After acidification of the NaOH extract, the solution was extracted with EtOAc. The extract was dried and concentrated to give crude **20.** Sublimation (2 Torr) or recrystallization from 40% EtOH gave 0.072 g (40%) of **20** as a pale yellow powder:[5,19] mp 259–262 °C; ν (Nujol) 3400, 3200 cm^{-1}; λ (EtOH) 253 (infl), 259, 303, 309 (infl), 316 (infl), 328 nm (infl); λ (pH 11) 246, 335 nm; δ ($CDCl_3$ + Me_2SO-d_6) 6.7–6.9 (m, 2 H), 7.1–7.4 (m, 3 H), 7.7–8.0 (m, 2 H).

Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.41; H, 4.70; N, 7.28.

B. Compound **5** (0.215 g) and 0.16 g of $TsOH-H_2O$ in 9 ml of dioxane was heated under reflux for 2 h. Work-up as described above gave 0.087 g (55%) of **20.**

2-Hydroxy-9-methylcarbazole (21). A solution of 0.264 g of **6** and 0.2 g of $TsOH-H_2O$ in 12 ml of dioxane was heated under reflux for 3 h. Work-up as described above gave 0.106 g (54%) of **21** as a colorless solid:[5] mp 164–165° (from 40% EtOH); ν (Nujol) 3320 cm^{-1}; λ (EtOH) 239, 256 (infl), 262, 265 (infl), 304, 320, 335 nm; λ (pH 11) 249, 336 nm; *m/e* 197 (M^+), 168; δ ($CDCl_3$) 3.72 (s, 3 H), 6.5–6.8 (m, 2 H), 7.2–7.4 (m, 3 H), 7.8–8.1 (m, 2 H).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.70; H, 5.63; N, 7.07.

Treatment of 6 with TsOH in MeCN at 50 °C. A solution of 0.132 g of **6** and 0.19 g of $TsOH-H_2O$ in 2 ml of MeCN was heated at 50 °C for 1.5 h. After the addition of $NaHCO_3$ solution, the mixture was evaporated to remove the MeCN and extracted with CH_2Cl_2. The extract was shaken with 10% NaOH. From the NaOH layer 34 mg (34%) of **21** was isolated. The CH_2Cl_2 layer was washed with H_2O and evaporated, and the residue was chromatographed on a silica gel column. Elution with CCl_4–$CHCl_3$ (5:1) gave 25 mg (22%) of **9-methyl-2-methylthiocarbazole (22):** mp 118–120° (from 90% EtOH); λ (EtOH) 240.5, 253, 260.5, 302 (infl), 313, 334 (infl), 344 nm (infl); *m/e* 227 (M^+), 212, 194; δ (CCl_4) 2.50 (s, 3 H), 3.70 (s, 3 H), 6.9–7.3 (5 H), 7.7–8.0 (2 H).

Anal. Calcd for $C_{14}H_{13}NS$: C, 73.99; H, 5.77; N, 6.16; S, 14.08. Found: C, 74.17; H, 5.62; N, 6.03; S, 13.87.

9-Methylcarbazole (23). A mixture of 50 mg of **22** and ca. 1 ml of Raney Ni in 8 ml of EtOH was heated under reflux for 3 h. After removal of Ni by filtration, the filtrate was evaporated to leave a solid, which was recrystallized form EtOH to give 21 mg of **23,**[20] mp 81–83 °C.

2-Methoxy-9-methylcarbazole (24). A solution of 0.264 g of **6** and 0.38 g of $TsOH-H_2O$ in 12 ml of Me_2CO and 1.2 ml of MeOH was heated under reflux for 5 h. The solution was cooled, neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove the organic solvents, and extracted with $CHCl_3$. The extract was dried and evaporated to leave crude **24.** Purification by passing in CCl_4–$CHCl_3$ (5:1) through silica gel gave 0.1 g (47%) of **24** as a solid.[5] Recrystallization from 90% EtOH gave colorless needles: mp 97–98 °C; λ (EtOH) 255 (infl), 261, 264 (infl), 302, 320, 333 nm; *m/e* 211 (M^+), 196, 168; δ ($CDCl_3$) 3.72 (s, 3 H), 3.90 (s, 3 H), 6.7–6.9 (m, 2 H), 7.0–7.4 (m, 3 H), 7.8–8.1 (m, 2 H).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.56; H, 6.20; N, 6.63. Found: C, 79.76; H, 6.24; N, 6.37.

2-Ethoxy-9-methylcarbazole (25). When EtOH was used in the place of MeOH in the foregoing experiment, 0.09 g (40%) of **25** was isolated. Recrystallization from 90% EtOH gave colorless needles: mp 76–78 °C; *m/e* 225 (M^+), 197, 168; δ ($CDCl_3$) 1.50 (t, 3 H), 3.77 (s, 3 H), 4.18 (q, 2 H), 6.7–6.9 (m, 2 H), 7.1–7.5 (m, 3 H), 7.9–8.1 (m, 2 H).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.00; H, 6.72; N, 6.26.

2,9-Dimethyloxazolo[5,4-*b*]carbazole (28). A solution of 0.16 g of 8 and 0.19 g of $TsOH-H_2O$ in 6 ml of MeCN was heated under reflux for 3.5 h. The solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove MeCN, and extracted with $CHCl_3$. The extract was dried and evaporated to leave crude **28,** which was chromatographed on a silica gel column. Elution with benzene–$CHCl_3$ (1:1) gave 0.095 g (80%) of a solid, which was re-

crystallized from EtOH: mp 180–181 °C; *m/e* 236 (M^+); λ (EtOH) 232, 239, 248, 278, 308, 338, 353 nm; δ ($CDCl_3$) 2.70 (s, 3 H), 3.90 (s, 3 H), 7.1–7.6 (4 H), 8.1 (d, 1 H, J = 7 Hz), 8.23 (s, 1 H).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.15; H, 4.93; N, 11.68.

2-Hydroxy-3-methylcarbazole (26). A solution of 0.526 g of **10** and 0.16 g of TsOH–H_2O in 10 ml of MeCN was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in Et_2O, washed with $NaHCO_3$ solution, and extracted with 10% NaOH solution. The aqueous layer was acidified with HCl and extracted with Et_2O, dried, and evaporated to give 0.197 g (50%) of **26**:[8] mp 237–240 °C (from cyclohexane–EtOH); ν (Nujol) 3500, 3375, 1630, 1605 cm^{-1}; *m/e* 197 (M^+); δ (Me_2SO-d_6) 2.28 (s, 3 H), 6.88 (s, 1 H), 7.00–7.40 (m, 3 H), 7.70 (s, 1 H), 7.86 (1 H).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.04; H, 5.63; N, 6.98.

9-Benzyl-2-methoxy-4-methylcarbazole (27). A solution of 0.353 g of **11** and 0.38 g of TsOH–H_2O in 12 ml of Me_2CO containing 1.2 ml of MeOH was heated under reflux for 6 h. After being cooled, the solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove the solvent, and extracted with CH_2Cl_2. The extract was dried and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with hexane–CH_2Cl_2 (2:1) gave 0.065 g (23%) of **27**. Recrystallization from EtOH gave colorless needles: mp 164.5–166.5 °C; *m/e* 301 (M^+); δ ($CDCl_3$) 2.85 (s, 3 H), 3.82 (s, 3 H), 5.45 (s, 2 H), 6.65 (s, 2 H), 7.1–7.4 (m, 8 H), 8.0–8.25 (m, 1 H).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.52; H, 6.36; N, 4.60.

2,5-Dimethyloxazolo[4,5-*b*]carbazole (30). A solution of 0.12 g of **29** and 0.083 g of TsOH–H_2O in 3 ml of MeCN was heated under reflux for 1 h. Work-up as described above gave 3 mg (3.4%) of **30** as a solid, which was recrystallized from EtOH: mp 200–202 °C; *m/e* 236 (M^+); λ (EtOH) 244, 251, 260 (infl), 272, 300, 306 (infl), 312 nm.

2-(1-Methyl-3-indolyl)ethyl Methylsulfinyl(phenylcarbamoyl)methyl Ketone (31). To an ice-cooled solution of the Na salt of **6**, prepared from 0.526 g of **6** and 57 mg of NaH in 15 ml of THF, 0.24 g of phenyl isocyanate was added dropwise with stirring. The stirring was continued for 70 min at room temperature, and then the mixture was poured into 50 ml of saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated to leave 0.718 g (94%) of **31**, which was recrystallized from EtOH: mp 136–139°; ν (Nujol) 1715, 1665 cm^{-1}.

Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.33; S, 8.37. Found: C, 66.10; H, 5.81; N, 7.22; S, 8.52.

2-(1-Methyl-3-indolyl)ethyl Methylsulfinyl(ethylcarbamoyl)methyl Ketone (32). Compound **32** was synthesized from 0.526 g of **6** and 0.142 g of ethyl isocyanate in 97% yield (0.65 g) as described above: mp 116–117° (from EtOAc); ν (Nujol) 3250, 1717, 1655 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.06; H, 6.63; N, 8.38; S, 9.57. Found: C, 60.91; H, 6.61; N, 8.34; S, 9.52.

Treatment of 31 with TsOH in MeCN. A solution of 0.382 g (1 mmol) of **31** and 0.76 g (4 mmol) of TsOH–H_2O in 10 ml of MeCN was heated under reflux for 1 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2. The solution was washed with $NaHCO_3$ solution and H_2O, dried, and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with benzene–EtOAc (15:1) gave 95 mg (30%) of **2-hydroxy-9-methylcarbazole-1-carboxanilide (33):** mp 247–249 °C (from EtOH); ν (Nujol) 3360, 3240, 1640 cm^{-1}; *m/e* 316 (M^+), 223 (base peak); δ (Me_2SO-d_6) 3.70 (s, 3 H), 6.7–8.0 (12 H), 9.75 (s, 1 H).

Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.71; H, 5.14; N, 9.02.

The elution was continued to isolate 0.163 g (45%) of **3,4-dioxo-6-methyl-3a-methylthio-5-phenyl-1,2,3,3a,4,5,5a,6-octahydrocyclopent[*c*]pyrrolo[2,3-*b*]indole (35):** mp 185–187° (from MeOH); ν (Nujol) 1745, 1690 cm^{-1}; *m/e* 364 (M^+); δ ($CDCl_3$) 2.28 (s, 3 H), 2.35–2.9 (4 H), 2.60 (s, 3 H), 5.40 (s, 1 H), 6.4–7.4 (9 H).

Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69; S, 8.78. Found: C, 69.06; H, 5.51; N, 7.73; S, 8.77.

Treatment of 32 with TsOH. A. A solution of 67 mg of **32** and 57 mg of TsOH–H_2O in 6 ml of MeCN was heated under reflux for 2 h. After the addition of $NaHCO_3$ solution, MeCN was evaporated, and the residue was extracted with CH_2Cl_2. The extract was dried and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with benzene–EtOAc (6:1) gave 22 mg (41%) of ***N*-ethyl-2-hydroxy-9-methylcarbazole-1-carboxamide (34):** mp 224–226° (from EtOH); ν (Nujol) 3255, 1639 cm^{-1}; *m/e* 268 (M^+), 223 (base peak), 195, 167.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.48. Found: C, 71.66; H, 6.00; N, 10.41.

The elution was continued to isolate 21 mg (33%) of **3,4-dioxo-5-ethyl-6-methyl-3a-methylthio-1,2,3,3a,4,5,5a,6-octahydrocyclopent[*c*]pyrrolo[2,3-*b*]indole (36):** mp 160–161° (from MeOH); ν (Nujol) 1745, 1685 cm^{-1}; δ ($CDCl_3$) 1.20 (t, 3 H, J = 7 Hz), 2.04 (s, 3 H), 2.15–2.8 (4 H), 3.06 (s, 3 H), 3.3–3.7 (2 H), 4.88 (s, 1 H), 6.5–7.5 (4 H).

Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.54; H, 6.37; N, 8.86; S, 10.11. Found: C, 64.25; H, 6.40; N, 8.77, S, 10.08.

B. A solution of 0.165 g (0.5 mmol) of **32** and 15 mg of TsOH–H_2O in 10 ml of dioxane was heated at 50 °C for 5 h. Work-up as described above gave two fractions. The first fraction was 70 mg (44%) of ***N*-ethyl-2-oxo-9-methyl-1-methylthio-1,2,3,4-tetrahydrocarbazole-1-carboxamide (37):** mp 139–141 °C (from EtOH); ν (Nujol) 3300, 1700, 1660 cm^{-1}; δ ($CDCl_3$) 1.10 (t, 3 H), 2.00 (s, 3 H), 2.7–3.1 (m, 6 H), 3.75 (s, 3 H), 7.1–7.7 (m, 4 H).

Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.54; H, 6.37; N, 8.86; S, 10.11. Found: C, 64.46; H, 6.41; N, 8.83; S, 10.15.

The second fraction was 63 mg (40%) of **36**.

2-(5-Phenyl-2-pyrrolyl)ethyl Methylsulfinylmethyl Ketone (40). Compound **40** was prepared from 2.4 g of ethyl 5-phenylpyrrole-2-propionate[11] and Me_2SO: yield 2.1 g; mp 134–136 °C (from EtOAc); ν (Nujol) 3250, 1715 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.44; H, 6.22; N, 5.09; S, 11.62. Found: C, 65.54; H, 6.32; N, 5.22; S, 11.36.

2-(5-Phenyl-2-pyrrolyl)ethyl Methylsulfinyl(phenylcarbamoyl)methyl Ketone (41). Compound **41** was prepared from 0.275 g of **40** and 0.12 g of phenyl isocyanate as described above: yield 0.19 g; mp 117 °C (from Et_2O); ν (Nujol) 3400, 3240, 1710, 1670, 1040 cm^{-1}.

Anal. Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.99; H, 5.62; N, 7.10; S, 8.11. Found: C, 67.03; H, 5.63; N, 7.07; S, 8.33.

4-Methylthio-5-oxo-2-phenyl-4,5,6,7-tetrahydroindole (42). A solution of 0.138 g of **40** and 0.038 g of TsOH–H_2O in 10 ml of THF was heated under reflux for 1 h. The solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo to remove THF, and extracted with CH_2Cl_2. The extract was dried and evaporated to leave crude **42**, which was purified on a silica gel column eluting with $CHCl_3$ to give 0.081 g (63%) of a solid. Recrystallization from EtOH gave colorless needles: mp 139–141 °C; ν (Nujol) 3320, 1690 cm^{-1}; *m/e* 257 (M^+); δ ($CDCl_3$) 2.12 (s, 3 H), 2.35–2.56 (m, 1 H), 2.92–3.08 (m, 2 H), 3.24–3.50 (m, 1 H), 4.08 (s, 1 H), 6.40 (d, 1 H, J = 2 Hz), 7.18–7.5 (5 H), 8.35 (broad s, 1 H).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.02; H, 5.88; N, 5.44; S, 12.44. Found: C, 70.12; H, 5.73; N, 5.42; S, 12.57.

5-Methoxy-2-phenylindole (43). A solution of 0.137 g of **40** and 0.095 g of TsOH–H_2O in 15 ml of MeOH was heated under reflux for 40 min. To this solution, $NaHCO_3$ solution was added, and the neutralized solution was concentrated to remove MeOH and then extracted with CH_2Cl_2. The extract was dried and evaporated to leave crude **43**, which was decolorized by passing in benzene through a column of Al_2O_3 to give 0.088 g (80%) of **43**. Recrystallization from 60% EtOH gave colorless needles, mp 164–166 °C.[21]

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.66; H, 5.82; N, 6.02.

5-Ethoxy-2-phenylindole (44). A solution of 0.137 g of **40** and 0.095 g of TsOH–H_2O in 15 ml of EtOH was heated under reflux for 40 min. Work-up as described for **43** gave 0.085 g (72%) of **44**, mp 136–137 °C.[21]

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.07; H, 6.32; N, 5.69.

5-Hydroxy-2-phenylindole-4-carboxanilide (45). A solution of 0.198 g of **41** and 0.1 g of TsOH–H_2O in 10 ml of *i*-PrOH was heated under reflux for 1 h. To this solution was added $NaHCO_3$ solution, and the neutralized solution was concentrated and then extracted with CH_2Cl_2. The extract was dried and evaporated to give crude **45**, which was purified on a column of silica gel eluting with $CHCl_3$ to give 0.15 g (91%) of a solid. Recrystallization from benzene gave needles: mp 206–208 °C; *m/e* 328 (M^+); ν (Nujol) 3450, 1635 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.98; H, 4.71; N, 8.70.

2-(2-Thienyl)ethyl Methylsulfinylmethyl Ketone (46). Compound **46** was synthesized from methyl 2-thiophenepropionate[22] and Me_2SO in 70% yield as a pale yellow oil: ν (neat) 1700, 1030 cm^{-1}; δ ($CDCl_3$) 2.60 (s, 3 H), 3.00 (q, 4 H, J = 4 Hz), 3.72 (s, 2 H), 6.75–7.15 (3 H).

2-(2-Thienyl)ethyl Methylsulfinyl(phenylcarbamoyl)methyl Ketone (47). Compound **47** was synthesized from the Na salt of 0.432 g of **46** and 0.24 g of phenyl isocyanate in THF. Work-up as described for **41** gave 0.6 g of **47**, which was recrystallized from EtOAc: mp 127–129 °C; ν (Nujol) 1715, 1670 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}NO_3S_2$: C, 57.31; H, 5.11; N, 4.18; S, 19.08. Found: C, 56.74; H, 5.01; N, 4.09; S, 18.68.

2-(2-Thienyl)ethyl 1-Methylsulfinyl-2-methoxycarbonylethyl Ketone (48). To an ice-cooled solution of the Na salt of **46**, prepared from 0.432 g of **46** and 0.06 g of NaH in 10 ml of THF, 0.32 g of methyl bromoacetate in 3 ml of THF was added with stirring. After being stirred for 1 h at room temperature, the mixture was concentrated in vacuo and then diluted with H_2O. The solution was acidified with HCl to pH 5 and extracted with $CHCl_3$. The extract was dried and concentrated to leave crude **48**, which was purified on a silica gel column eluting with $CHCl_3$–EtOAc (1:1) to give 0.28 g of **48** as an oil: ν (neat) 1730, 1700, 1050 cm^{-1}.

4-Methylthio-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (49). A solution of 0.23 g of **46** and 0.228 g of CF_3CO_2H in 6 ml of benzene was heated under reflux for 2 h. The solution was cooled, washed with $NaHCO_3$ solution, dried, and evaporated to leave crude **49**, which was purified on a silica gel column eluting with benzene to give 0.1 g (50%) of **49** as an oil: *m/e* 198 (M^+), 151, 150, 123; ν (neat) 1700 cm^{-1}; δ ($CDCl_3$) 2.05 (s, 3 H), 3.0–3.3 (4 H), 4.02 (s, 1 H), 6.87 (d, 1 H, J = 5 Hz), 7.08 (d, 1 H, J = 5 Hz).

Treatment of 46 with TsOH in MeCN. A solution of 0.27 g of **46** and 0.44 g of TsOH–H_2O in 8 ml of MeCN was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, and the solution was washed with $NaHCO_3$ solution and then extracted with 10% NaOH. From the CH_2Cl_2 layer **51** and **54** were isolated (see below).

The aqueous layer was acidified with 10% HCl and extracted with CH_2Cl_2. The extract was dried and concentrated to give 0.101 g (56%) of **5-hydroxybenzo[*b*]thiophene (50)**,[23] which was recrystallized from hexane to afford colorless plates: mp 103–105 °C; *m/e* 150 (M^+), 122, 121.

Anal. Calcd for C_8H_6OS: C, 64.00; H, 4.03; S, 21.31. Found: C, 63.71; H, 3.92; S, 21.15.

The initial CH_2Cl_2 layer was dried and concentrated to leave an oil (0.043 g), which was a mixture of 14% of **5-methylthiobenzo[*b*]thiophene (51)**, *m/e* 180 (M^+), 165, 121, δ ($CDCl_3$) 2.47 (s, 3 H), and 7% of **2-(2-thienyl)ethyl (bismethylthio)methyl ketone (54)**, *m/e* 107 [$CH(SMe)_2$], δ ($CDCl_3$) 1.95 (s, 6 H), 4.25 (s, 1 H).

5-Methoxybenzo[*b*]thiophene (52). A solution of 0.216 g of **46** and 0.978 g of CCl_3CO_2H in 12 ml of MeCN containing 0.4 ml of MeOH was heated under reflux for 4 h. After being cooled, the solution was neutralized with $NaHCO_3$ solution, concentrated in vacuo, and extracted with CH_2Cl_2. The extract was dried and chromatographed on a column of silica gel eluting with CCl_4 to give 36 mg (22%) of **52** as a colorless solid:[24] mp 38–40 °C; *m/e* 164 (M^+), 149, 121.

5-Hydroxybenzo[*b*]thiophene-4-carboxanilide (53). A solution of 0.224 g of **47** and 0.126 g of TsOH–H_2O in 12 ml of benzene was heated under reflux for 1 h. The solution was cooled, washed with $NaHCO_3$ solution, dried, and evaporated to leave crude **53**, which was purified on a silica gel column eluting with $CHCl_3$ to give 0.1 g (55%) of **53**. Recrystallization from EtOH afforded colorless scales: mp 190–192°; ν (Nujol) 3320, 3120, 1630 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.91; H, 4.12; N, 5.20. Found: C, 67.08; H, 4.00; N, 5.11.

2,3-Dihydro-2-oxobenzo[*b*]thieno[5,4-*b*]furan (55). A solution of 0.288 g of **48** and 0.19 g of TsOH–H_2O in 12 ml of benzene was heated under reflux for 1 h. After being cooled, the solution was washed with $NaHCO_3$ solution, dried, and evaporated. The residue was purified on a silica gel column eluting with benzene to give 0.048 g (25%) of **55**, which was recrystallized from benzene–hexane: mp 121–123 °C; ν (Nujol) 1790 cm^{-1}; *m/e* 190 (M^+), 162, 134.

Anal. Calcd for $C_{10}H_6O_2S$: C, 63.16; H, 3.18; S, 16.83. Found: C, 63.28; H, 3.18; S, 16.60.

1-Acetamido-2-(2-thienyl)ethyl Methylsulfinylmethyl Ketone (56). Compound **56** (3.57 g) was synthesized from 5.76 g of *N*-acetylthiophene-2-alanine methyl ester[25] and 1.86 g of NaH in 40 ml of Me_2SO: mp 132 °C (from EtOAc); ν (Nujol) 3250, 3070, 1715, 1650 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_3S_2$: S, 23.40. Found: S, 22.69.

2-Methyloxazolo[5,4-*f*]benzo[*b*]thiophene (57). A solution of 0.25 g of **56** and 0.39 g of TsOH–H_2O in 9 ml of MeCN was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$, and the solution was washed with $NaHCO_3$ solution, dried, and concentrated to give **57**, which was purified by passing in benzene through an Al_2O_3 column to give 0.09 g (53%) of **57**: mp 76–77 °C (from hexane); ν (Nujol) 1618, 1600, 1565 cm^{-1}; *m/e* 189 (M^+), 120; δ ($CDCl_3$) 2.67 (s, 3 H), 7.45 (q, 2 H), 7.86 (s, 1 H), 8.15 (s, 1 H).

Anal. Calcd for $C_{10}H_7NOS$: S, 16.92. Found: S, 16.63.

Registry No.—**5**, 38499-75-1; **5** K salt, 57900-77-3; **6**, 57900-78-4; **6** Na salt, 57900-79-5; **7**, 57900-80-8; **8**, 38499-79-5; **9** isomer 1, 57900-81-9; **9** isomer 2, 57900-82-0; **10** isomer 1, 57900-83-1; **10** isomer 2, 57951-58-3; **11** isomer 1, 57900-84-2; **11** isomer 2, 57900-85-3; **12**, 38499-77-3; **13**, 38499-78-4; **14**, 51894-58-7; **15**, 38499-80-8; **16**, 57900-86-4; **17**, 57900-87-5; **18** isomer 1, 57900-88-6; **18** isomer 2, 57900-89-7; **19**, 40429-00-3; **20**, 86-79-3; **21**, 51846-67-4; **22**, 57900-90-0; **23**, 1484-12-4; **24**, 39027-93-5; **25**, 51846-68-5; **26**, 24224-30-4; **27**, 57900-91-1; **28**, 51846-69-6; **29** isomer 1, 57900-92-2; **29** isomer 2, 57900-93-3; **30**, 51846-71-0; **31**, 57900-94-4; **32**, 57900-95-5; **33**, 57900-96-6; **34**, 57900-97-7; **35**, 57900-98-8; **36**, 57900-99-9; **37**, 57901-00-5; **40**, 57901-01-6; **41**, 57901-02-7; **42**, 51846-54-9; **43**, 5883-96-5; **44**, 23746-83-0; **45**, 51846-55-0; **46**, 57901-03-8; **46** Na salt, 57901-04-9; **47**, 57901-05-0; **48**, 57901-06-1; **49**, 51846-59-4; **50**, 19301-35-0; **51**, 51846-60-7; **52**, 20532-30-3; **53**, 51846-61-8; **54**, 51846-62-9; **55**, 51846-63-0; **56**, 57901-07-2; **57**, 51846-65-2; Me_2SO, 67-68-5; methyl indole-3-propionate, 5548-09-4; methyl (1-methyl-3-indolyl)propionate, 57901-08-3; benzyl chloride, 100-44-7; methyl 3-(1-benzyl-3-indolyl)propionate, 57901-09-4; *N*-acetyl-*dl*-tryptophan methyl ester, 16108-06-8; methyl 2-acetamido-3-(1-methyl-3-indolyl)propionate, 57901-10-7; ethyl 3-(3-indolyl)-2-methylpropionate, 57901-11-8; *N*-(3-indolyl-1-ethyl)-*N*-isopropylamine, 14121-10-9; ethyl 3-(1-benzyl-3-indolyl)butyrate, 57901-12-9; diethyl malonate, 105-53-3; ethyl 2-acetamido-3-(1-methyl-2-indolyl)propionate, 57901-13-0; ethyl 2-acetamido-3-(2-indolyl)propionate, 27442-71-3; CCl_3CO_2H, 76-03-9; TsOH, 104-15-4; MeOH, 67-56-1; EtOH, 64-17-5; phenyl isocyanate, 103-71-9; ethyl isocyanate, 109-90-0; ethyl 5-phenylpyrrole-2-propionate, 57901-14-1; methyl 2-thiophenepropionate, 16862-05-8; CF_3CO_2H, 76-05-1; *N*-acetylthiophene-2-alanine methyl ester, 57901-15-2.

References and Notes

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Sulfur-Containing Carbohydrates. Synthesis of 1,3,4,6-Tetrathio-D-iditol[1,2]

Gifford E. McCasland,*[3a] Alberto B. Zanlungo, and Lois J. Durham[3b]

Departments of Chemistry, University of San Francisco, San Francisco, California 94117, and Stanford University, Stanford, California 94305

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A series of analogues of D-iditol and its derivatives have been prepared, in which two, or four, of the hexitol oxygen atoms are replaced by sulfur. The 1,2;5,6-di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio derivative (formula **1**, mp 127 °C) of 3,4-dithio-D-iditol was oxidized to the corresponding dithiocarbonate (**2**). The trithiocarbonate **1** was also reduced to the dithiol diketal (**7**) which was characterized by conversion to the di-*S*-acetate (**8**) and the *O,O,S*-triketal (**9**). The trithiocarbonate diketal (**1**) on reaction with anhydrous hydrogen bromide–acetic acid was converted to the 1,6-dibromide 2,5-di-*O*-acetate (**10**). The dithiocarbonate diketal (**2**) similarly was transformed into the dibromide diacetate **5**. The trithiocarbonate dibromide (**10**) on prolonged heating with potassium thiolacetate surprisingly gave the dithiocarbonate tetraacetate derivative (**6**) of 1,3,4,6-tetrathio-D-iditol; this was confirmed by preparation of **6** from the dithiocarbonate dibromide (**5**) and potassium thiolacetate. The dithiocarbonate di-*O*-acetate di-*S*-acetate (**6**) on reduction gave free 1,3,4,6-tetrathio-D-iditol (**11**), mp 87 °C, which was converted to its hexaacetate **12**, mp 97 °C. The above di-*O*-isopropylidene dithiol (**7**) was also used to prepare its di-*S*-benzyl derivative, **15**, and the related tetrol (**13**) and tetraacetate (**14**). The tetrol **13** was also converted to the 1,6-di-*O*-trityl-2,5-di-*O*-acetyl derivative **16**. Since the trityl, acetyl, and *S*-benzyl protective groups can easily be removed when desired, the compound **16** should be a useful intermediate for preparation of pentathio- and hexathiohexitols.

For two decades, one of the most rapidly expanding fields of organic chemistry has been the preparation of sulfur analogues of organic oxygen compounds, and in particular of carbohydrates. Since most reported sulfur analogues of carbohydrates have contained only one or two sulfur atoms, we have in recent years concentrated our attention on efforts to prepare analogues in which most or all of the oxygen atoms of well-known carbohydrates would be replaced by sulfur (polythio- and perthiocarbohydrates). Most of the carbohydrates we have chosen for emulation have been hexitols or cyclohexitols (inositols).[2,4]

In the present article, we describe the preparation of dithio and tetrathio analogues of D-iditol and many of its derivatives. Each product reported has been extensively characterized, and we are hopeful that some of these compounds will have valuable physical, chemical, and especially biological properties.

The starting material for our present studies was the diisopropylidene trithiocarbonate derivative (formula **1**) of 3,4-dithio-D-iditol.[2b] This yellow, crystalline compound, mp 126–127 °C, on permanganate oxidation gave the corresponding, colorless dithiocarbonate, **2**, which has very nearly the same melting point, but differs markedly in its optical rotation and infrared spectrum (C=O vs. C=S).

The trithiocarbonate **1** was also converted, by lithium aluminum hydride reduction, to the di-*O*-isopropylidene derivative, **7**, of 3,4-dithio-D-iditol, mp 138 °C. This product was transformed in the usual manner to its di-*S*-acetate **8**, mp 116 °C, and to the triisopropylidene derivative, **9**, mp 80 °C. The ^{1}H NMR spectrum of **9** revealed sharply different chemical shifts for the *O*- and *S*-isopropylidene methyl singlets (δ 1.35 and 1.92 ppm, respectively).

Attempted mild acid hydrolysis of **7** (and presumably of **9**) to the free dithiohexitol surprisingly gave instead the mono-*S*-isopropylidene derivative, **17**, mp 105 °C. Isotopic studies using acetone-d_6 showed that this result, in the case of **7**, is due to fast reaction of the SH groups with (hydrolytically liberated) acetone in the reaction mixture, to form the more stable dithiolane ring. The product structure was established by the NMR methyl group chemical shifts mentioned above.[4d]

Our purpose was next to transform one of these intermediates, e.g., **7**, having C–S bonds at positions 3 and 4, to a polythio or preferably hexathiohexitol, having C–S bonds at some or all of the remaining positions 1, 2, 5, and 6. It appeared that this might best be accomplished by introduction of a suitable bivalent substituent, such as thiocarbonyldithio, epithio, epoxy, or even a carbon–carbon double bond, at 1,2 and/or at 5,6.

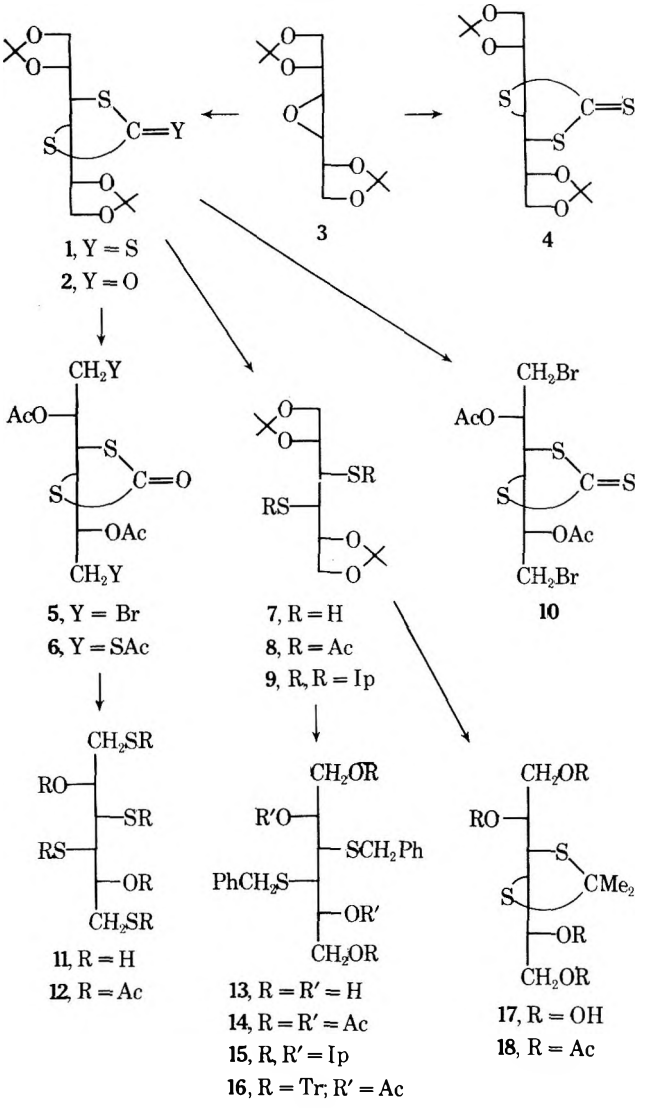
As a first step in this direction, the trithiocarbonate diketal, **1**, was converted by direct reaction with anhydrous hydrogen bromide–acetic acid to a 1,6-dibromide, isolated in the form of its 2,5-diacetate **10**, mp 102 °C, yellow crystals. The corresponding dithiocarbonate dibromide diacetate, **5**, colorless crystals, mp 108 °C, was prepared from the dithiocarbonate **2** in the same manner. (In previous work, we have found that dithiocarbonates sometimes crystallize more easily, and give better yields in subsequent reactions.)

The dithiocarbonate dibromide, **5**, on prolonged heating with potassium thiolacetate in acetone, gave the expected dithiocarbonate tetraacetate derivative, **6**, of 1,3,4,6-tetrathio-D-iditol, colorless plates, mp 116 °C. Similar reaction of the trithiocarbonate dibromide **10** gave a brown syrup, which was purified by chromatography using silica gel. The crystalline product then isolated, mp 116 °C, surprisingly was identical with the above dithiocarbonate tetraacetate, **6**. The oxygen atom in the carbonyldithio group conceivably may be derived from the thiolacetate, acetone, water, ethyl acetate, or silica gel used in the procedure (see Experimental Section); however, no really good explanation is yet available.

In order to obtain one of the desired polythioalditol final products, the tetrathiohexitol dithiocarbonate tetraacetate **6** was reduced with lithium aluminum hydride under dry nitrogen (to prevent oxidation of free SH groups). The product, 1,3,4,6-tetrathio-D-iditol (**11**), was obtained as colorless, almost odorless plates, mp 87 °C, specific rotation −153°. This tetrathiohexitol appears to be somewhat less polar than ordinary hexitols, as indicated by its solubility in boiling (but not cold) isopropyl ether. The di-*O*-acetate tetra-*S*-acetate derivative **12**, mp 97 °C, was prepared in the usual manner.

We next attempted to introduce mercapto (or other suit-

Chart I



able sulfur) groups into the two remaining positions, 2 and 5. For this purpose, the 1,6-dibromide (**5** or **10**), or 1,6-di(acetylthio) derivative (**6**, **11**, or **12**) seemed especially suitable. However, we have not yet been able to prepare the 1,2 (and/or 5,6) epithio, thiocarbonyldithio, etc., intermediates which presumably could be transformed easily into pentathio- or hexathiohexitols.

Some preliminary work has been done on an alternative approach. This involves using *S*-benzyl groups as temporary protective groups for the two SH groups at positions 3 and 4, e.g., in the intermediate **7**. The *S*-benzyl group is easily removed when desired, by reductive fission, for example in our previously reported preparation of a mercaptodeoxyinositol.[4c]

The di-*O*-isopropylidene derivative **7** of 3,4-dithio-D-iditol accordingly was treated with benzyl bromide and sodium hydride in dimethylformamide. The di-*S*-benzyl product **15** was obtained as colorless needles, mp 106 °C. By mild acid hydrolysis, this intermediate was converted to the di-*S*-benzyl dithiohexitol **13**, mp 101 °C. This compound was converted to its tetraacetate, **14**, mp 110 °C, in the usual manner.

The di-*S*-benzyl tetrol **13** was next converted, in the usual manner, to its 1,6-bis(triphenylmethyl) derivative, isolated as the 2,5-diacetate **16**, mp 160 °C. This should be a useful intermediate, since either the trityl or acetyl protective group is easily removed under mild conditions, permitting synthetic operations on the corresponding free hydroxyl groups. After introduction of sulfur at positions 1, 2, 5, and 6, the *S*-benzyl protective groups could be removed.

Since, unfortunately, our laboratory has had to discontinue research on sulfur-containing carbohydrates, we are making these preliminary results on *S*-benzyl derivatives available, for possible use by others working in this field.

Experimental Section

All melting points (corrected) were measured on a Nalge-Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. NMR spectra were recorded and integrated with Varian A-60D and/or HR-100 spectrometers. Chemical shifts are given as parts per million (δ). Field sweep was used for 60-MHz and frequency sweep for 100-MHz NMR spectra. Infrared spectra were measured on a Perkin-Elmer Model 337 spectrometer. Evaporations were performed under reduced pressure. Acetone used was reagent grade.

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio-D-iditol (1). The crude product previously reported[2b] was recrystallized from *n*-hexane, giving yellow crystals: mp 126.5–127.5 °C; $[\alpha]^{23}D$ −328° (*c* 2.1, $CHCl_3$); NMR (100 MHz, $CDCl_3$) δ 1.37 (s, 6, isopropylidene methyl), 1.48 (s, 6, isopropylidene methyl); ir (KBr) 1060 (C=S), 1150, 1060, and 1040 cm^{-1} (1,3-dioxolane).

Anal. Calcd for $C_{13}H_{20}O_4S_3$: C, 46.40; H, 5.99; S, 28.59. Found: C, 46.29; H, 5.84; S, 28.42.

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-carbonyl-3,4-dithio-D-iditol (2). To a solution of 2.0 g of the above trithiocarbonate, mp 126–127 °C, in 60 ml of acetone, 5.2 g of powdered potassium permanganate was added in small portions, with cooling and stirring, during 2 h. After an additional 1 h, the mixture was filtered, and the residue washed with three 15-ml portions of acetone.

The combined filtrates were evaporated, and the solid residue extracted with three 15-ml portions of boiling benzene. The benzene extract was evaporated, giving 1.23 g (62%) of colorless plates: mp 126–127 °C; $[\alpha]^{23}D$ −196° (*c* 1.5, $CHCl_3$); ir (KBr) 1610 (C=O), 1155, 1060, and 1040 cm^{-1} (1,3-dioxolane); NMR ($CDCl_3$) δ 1.43 (s, 6, isopropylidene methyl), 1.53 (s, 6, isopropylidene methyl).

Anal. Calcd for $C_{13}H_{20}O_5S_2$: C, 48.73; H, 6.29; S, 20.01. Found: C, 48.53; H, 6.21; S, 19.93.

1,2;5,6-Di-*O*-isopropylidene-3,4-dithio-D-iditol (7). The procedure was similar to one of Iqbal and Owen.[5] Reduction of 12.8 g of the above trithiocarbonate (formula **1**, mp 126–127 °C) with lithium aluminum hydride gave 7.80 g (74%) of colorless needles (crystallized from *n*-hexane), mp 136–138 °C. A sample was recrystallized: mp 137.5–138 °C; $[\alpha]^{23}D$ −38° (*c* 1.4, $CHCl_3$); NMR (100 MHz, $CDCl_3$) δ 1.38 (s, 6, isopropylidene methyl), 2.12 (d, 2, –SH), 1.47 (s, 6, isopropylidene methyl).

A similar preparation reported by Iqbal and Owen,[5] mp 133–135 °C, $[\alpha]^{23}D$ −10° (*c* 3.6, $CHCl_3$), presumably contained some D-manno impurity.

1,2;5,6-Di-*O*-isopropylidene-3,4-di-*S*-acetyl-3,4-dithio-D-iditol (8). A 107-mg portion of the above dithiol (**7**) was acetylated with acetic anhydride in pyridine, in the usual manner, giving 125 mg of crude product, mp 101–104 °C. This was crystallized from 5 ml of *n*-hexane, giving 74 mg (54%) of colorless needles, mp 115.5–116 °C. A sample was recrystallized: mp 115.5–116 °C; $[\alpha]^{23}D$ +4.0° (*c* 1.6, $CHCl_3$); ir (KBr) 1690 (C=O), 1150, 1070, and 1060 cm^{-1} (1,3-dioxolane); NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 6, isopropylidene methyl), 1.40 (s, 6, isopropylidene methyl), 2.37 (s, 6, $-SCOCH_3$).

Anal. Calcd for $C_{16}H_{26}O_6S_2$: C, 50.77; H, 6.92; S, 16.94. Found: C, 50.90; H, 6.91; S, 16.84.

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-isopropylidene-3,4-dithio-D-iditol (9). A mixture of 500 mg of the above dithiol **7** with 10 ml of acetone (dried with Drierite, and containing 0.01% sulfuric acid) and 1.2 g of fresh Drierite was stirred for 2 days and filtered. The filtrate was poured into 5% sodium bicarbonate solution, and the resulting mixture extracted repeatedly with chloroform. The extract was washed with water, dried, and evaporated, giving a solid residue. By two recrystallizations from *n*-hexane, there was obtained 100 mg of colorless crystals, mp 72–80 °C; then 35 mg, mp 76–79 °C.

A somewhat purer product was obtained from the combined mother liquors by chromatography (Woelm silica gel, 25 × 1 cm column, eluted with 1:2 isopropyl ether–*n*-hexane). The resulting material (280 mg, 55%, mp 79–80 °C) was recrystallized, giving a

sample of mp 79.5–80 °C; $[\alpha]^{23}D$ −110° (c 1.8, $CHCl_3$); NMR ($CDCl_3$) δ 1.42 (s, 6, *O*-isopropylidene), 1.53 (s, 6, *O*-isopropylidene), 1.92 (s, 6, *S*-isopropylidene).

Anal. Calcd for $C_{15}H_{26}O_4S_2$: C, 53.86; H, 7.84; S, 19.17. Found: C, 54.16; H, 8.03; S, 19.14.

1,6-Dibromo- 1,6-dideoxy-2,5-di-*O*-acetyl-3,4-*S*-thiocarbonyldithio-D-iditol (10). A 1.0-g portion of the trithiocarbonate diketal (**1**) was dissolved in 10 ml of an anhydrous 32% solution of hydrogen bromide in acetic acid. After 1 h at 25 °C, the solution was poured with stirring into 10 ml of saturated sodium bicarbonate solution. The resulting syrup was separated by decantation and washed twice with water, causing it to crystallize: dry weight 1.20 g, mp 96–99 °C. The product was recrystallized from benzene–*n*-hexane, giving 1.0 g (77%) of yellow plates, mp 100–102 °C.

A sample recrystallized from benzene had mp 101–102 °C; $[\alpha]^{24}D$ −265° (c 1.5, $CHCl_3$); ir (KBr) 1715 (C=O), 1070 cm^{-1} (C=S); NMR ($CDCl_3$) δ 2.18 (s, 6, $-OCOCH_3$).

Anal. Calcd for $C_{11}H_{14}O_4Br_2S_3$: C, 28.33; H, 3.03; Br, 34.28; S, 20.62. Found: C, 28.36; H, 3.08; Br, 32.38; S, 19.72.

1,6-Dibromo-1,6-dideoxy-2,5-di-*O*-acetyl-3,4-*S*-carbonyldithio-D-iditol (5). Similar reaction of the dithiocarbonate diketal (**2**, 300 mg) gave a syrup. This syrup was taken up in 10 ml of chloroform, and the solution washed twice with water, dried, and evaporated. The resulting syrup was crystallized from benzene–*n*-hexane, giving 250 mg of colorless crystals, mp 105–106.5 °C. A sample was again recrystallized: mp 107.5–108 °C; $[\alpha]^{24}D$ −124° (c 0.6, $CHCl_3$); ir (KBr) 1720 (acetate ester C=O), 1640 cm^{-1} (carbonyldithio C=O); NMR ($CDCl_3$) δ 2.15 (s, 6, acetate methyl).

Anal. Calcd for $C_{11}H_{14}Br_2O_5S_2$: C, 29.35; H, 3.13; Br, 35.50; S, 14.24. Found: C, 29.56; H, 3.14; Br, 35.63; S, 14.13.

2,5-Di-*O*-acetyl-1,6-di-*S*-acetyl-3,4-*S*-carbonyl-1,3,4,6-tetrathio-D-iditol (6). A. From the Trithiocarbonate. A mixture of 320 mg of the trithiocarbonate dibromide (**10**), 350 mg of potassium thiolacetate, and 15 ml of acetone was boiled under reflux for 24 h. The cooled, filtered mixture was evaporated. The residual syrup was taken up in chloroform, and the solution washed, dried, and evaporated. The residual brown syrup was taken up in ethyl acetate (decolorized with charcoal) and the solution evaporated.

The resulting syrup was purified by chromatography, using a 60 × 1.5 cm column of Woelm silica gel. The column was eluted with *n*-hexane containing increasing concentrations (5–40%) of ethyl acetate. The "40%" eluate on evaporation yielded 35 mg of colorless needles, mp 114–115 °C. A sample recrystallized from isopropyl ether had mp 114.5–115.5 °C; ir (KBr) 1750 (acetate C=O), 1700 (*S*-acetyl C=O), 1650 cm^{-1} (*S*-carbonyl); NMR ($CDCl_3$) δ 2.11 (s, 6, *O*-acetate methyl), 2.40 (s, 6, *S*-acetate methyl); $[\alpha]^{23}D$ −104° (c 0.6, $CHCl_3$).

This compound, prepared from the trithiocarbonate **10**, surprisingly was found to be the dithiocarbonate (**6**), as confirmed by preparation from the dithiocarbonate **5**, see procedure B below.

Anal. Calcd for $C_{15}H_{20}O_6S_5$: C, 39.46; H, 4.42; O, 21.02; S, 35.11. Calcd for $C_{15}H_{20}O_7S_4$: C, 40.89; H, 4.58; O, 25.42; S, 29.11. Found: C, 40.77; H, 4.54; (O, 25.09); S, 29.60.

B. From the Dithiocarbonate. The reaction of 1.50 g of the dithiocarbonate dibromide was conducted by a procedure similar to procedure A; however, chromatography was not employed. A 630-mg (43%) yield of once-crystallized (from benzene–*n*-hexane) product was obtained, mp 114–115 °C. A sample recrystallized from benzene melted at 114.5–115.5 °C.

Anal. Found: C, 41.04; H, 4.67; S, 28.64.

The product was identical with that from the above procedure A.

1,3,4,6-Tetrathio-D-iditol (11). A 250-mg portion of the dithiocarbonate tetraacetate (**6**) was reduced with lithium aluminum hydride in ether, and the product isolated, in the usual manner. The crude product, a syrup, was crystallized from isopropyl ether, giving 75 mg (60%) of colorless, almost odorless plates, mp 85–86 °C. A sample was recrystallized: mp 86.5–87 °C; $[\alpha]^{23}D$ −153° (c 2.7, methanol); ir (KBr) 3150 (broad, –OH), 2545 cm^{-1} (–SH). (The usually weak –SH chromophore was strong here, because four –SH groups are present.)

Anal. Calcd for $C_6H_{14}O_2S_4$: C, 29.24; H, 5.73; S, 52.05. Found: C, 29.41; H, 5.64; S, 50.67.

2,5-Di-*O*-acetyl-1,3,4,6-tetra-*S*-acetyl-1,3,4,6-tetrathio-D-iditol (12). A 45-mg portion of the tetrathiohexitol **11** was treated with acetic anhydride and pyridine, in the usual manner. The crude product, a syrup, was crystallized from *n*-hexane, giving 72 mg (82%) of colorless needles, mp 94–95.5 °C. A sample was recrystallized: mp 96–96.5 °C; $[\alpha]^{23}D$ +86° (c 1.9, $CHCl_3$); ir (KBr) 1750 (*O*-acetate C=O), 1700 cm^{-1} (*S*-acetate C=O); NMR ($CDCl_3$) δ 2.08 (s, 6, *O*-acetate methyl), 2.32 (s, 6, $-CH_2SCOCH_3$ methyl), 2.37 (s, 6, $=CHSCOCH_3$ methyl).

Anal. Calcd for $C_{18}H_{26}O_8S_4$: C, 43.36; H, 5.26; S, 25.72. Found: C, 43.58; H, 5.21; S, 25.80.

1,2;5,6-Di-*O*-isopropylidene-3,4-di-*S*-benzyl-3,4-dithio-D-iditol (15). To 1.24 g of the dithiol **7** and 570 mg of sodium hydride in 40 ml of dry *N,N*-dimethylformamide, under dry nitrogen, with stirring, at 0 °C, 8.5 g of benzyl bromide was added dropwise during 10 min. The mixture was stirred at 25 °C for 4 h.

Excess hydride was cautiously destroyed by addition of methanol, and the mixture evaporated at 1.2 Torr, 70 °C (bath).

The residual syrup was processed with chloroform and water in the usual manner. The solid residue from evaporation of the chloroform extract was recrystallized from *n*-hexane, giving 1.40 g (83%) of colorless crystals, mp 100–103 °C.

A sample was recrystallized: mp 105–105.5 °C; $[\alpha]^{24}D$ +217° (c 0.6, $CHCl_3$); ir (KBr) 1580 and 700 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.32 and 1.43 (s, 6 and s, 6, isopropylidene methyl).

Anal. Calcd for $C_{26}H_{34}O_4S_2$: C, 65.80; H, 7.22; S, 13.49. Found: C, 65.74; H, 7.30; S, 13.46.

3,4-Di-*S*-benzyl-3,4-dithio-D-iditol (13). A 900-mg portion of the diketal **15** was treated with warm ethanol containing a little 12 M hydrochloric acid, and the product isolated in the usual manner. The crude product, a syrup, was crystallized from benzene–petroleum ether (bp 30–60 °C), giving 730 mg of colorless needles, mp 98–99 °C. A sample was recrystallized from benzene: 660 mg (87%); mp 99.5–100.5 °C; $[\alpha]^{24}D$ −91° (c 1, methanol); ir (KBr) 1590 and 700 cm^{-1} (phenyl).

Anal. Calcd for $C_{20}H_{26}O_4S_2$: C, 60.90; H, 6.64; S, 16.24. Found: C, 60.86; H, 6.87; S, 16.14.

1,2,5,6-Tetra-*O*-acetyl-3,4-di-*S*-benzyl-3,4-dithio-D-iditol (14). A 70-mg portion of the tetrol **13** was treated with acetic anhydride–pyridine in the usual manner, giving 101 mg of crude solid product, mp 106–108.5 °C. This material was recrystallized from 1-butanol–petroleum ether (bp 50–60 °C), giving 68 mg (68%) of colorless plates: mp 109.5–110 °C; $[\alpha]^{23}D$ −75° (c 1.1, $CHCl_3$); ir (KBr) 1750 (C=O), 700 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.98 and 2.04 (s, 6 and s, 6, primary and secondary acetate methyl), 3.80 (s, 4, *S*-benzyl methylene).

Anal. Calcd for $C_{28}H_{34}O_8S_2$: C, 59.76; H, 6.09; S, 11.39. Found: C, 59.91; H, 6.25; S, 11.51.

2,5-Di-*O*-acetyl-1,6-di-*O*-trityl-3,4-di-*S*-benzyl-3,4-dithio-D-iditol (16). A 100-mg portion of the tetrol **13** was treated with excess triphenylmethyl chloride in dry pyridine for 2 days at 25 °C. Excess acetic anhydride was then added, and the mixture kept for 1 more day, then poured into water with stirring.

The crude solid product (220 mg) so obtained was purified by chromatography, using a 20 × 1 cm column of Woelm silica gel. The column was eluted with 50 ml of 1:3 acetone–*n*-hexane, giving 96 mg of solid product, on evaporation, mp 155–159 °C. Recrystallization from 95% ethanol afforded 72 mg of colorless plates, mp 159–160 °C. A sample was recrystallized: mp 159.5–160 °C; $[\alpha]^{23}D$ +34° (c 2.1, $CHCl_3$); ir (KBr) 1720 (C=O), 1580 and 700 cm^{-1} (phenyl).

Anal. Calcd for $C_{62}H_{58}O_6S_2$: C, 77.31; H, 6.07; S, 6.66. Found: C, 76.70; H, 6.13; S, 6.22.

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Registry No.—**1**, 51051-69-5; **2**, 57900-55-7; **5**, 57900-56-8; **6**, 57900-57-9; **7**, 32860-91-6; **8**, 57866-81-6; **9**, 57866-82-7; **10**, 57900-58-0; **11**, 57900-59-1; **12**, 57900-60-4; **13**, 57866-83-8; **14**, 57866-84-9; **15**, 57866-85-0; **16**, 57866-86-1.

References and Notes

(1) Presented to the Division of Carbohydrate Chemistry at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975.

(2) For preceding publication, see (a) A. B. Zanlungo and G. E. McCasland, *Carbohydr. Res.*, **38**, 352 (1974); see also (b) G. E. McCasland, A. B. Zanlungo, and L. J. Durham, *J. Org. Chem.*, **39**, 1462 (1974), and references cited therein.

(3) (a) To whom any communications should be addressed, at the University of San Francisco; (b) Stanford University.

(4) For earlier publications on sulfur analogues of alditols and cyclitols, see (a) G. E. McCasland, A. Furst, L. F. Johnson, J. N. Shoolery, and S. Furuta, *J. Org. Chem.*, **28**, 456 (1963); (b) G. E. McCasland, A. Furst, and S. Furuta, *J. Am. Chem. Soc.*, **85**, 2866 (1963); (c) *J. Org. Chem.*, **29**, 724 (1964); (d) G. E. McCasland and A. B. Zanlungo, *Carbohydr. Res.*, **17**, 475 (1971); (e) G. E. McCasland, A. K. M. Anisuzzaman, S. R. Naik, and L. J. Durham, *J. Org. Chem.*, **37**, 1201 (1972); (f) *Chem. Eng. News*, 51 (April 9, 1962).

(5) S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1030 (1960). It now appears that the dithiol product reported by these authors (and its trithiocarbonate precursor) may actually have been a mixture of the D-manno and D-ido isomers.

Alkane Diazotates. XXI. Ethanolysis and Thioethanolysis of Octane-2-diazotate[1]

Robert A. Moss*[2a] and Edward R. Grover[2b]

Wright and Rieman Laboratories, School of Chemistry, Rutgers University, The State University of New Jersey, New Brunswick, New Jersey 08903

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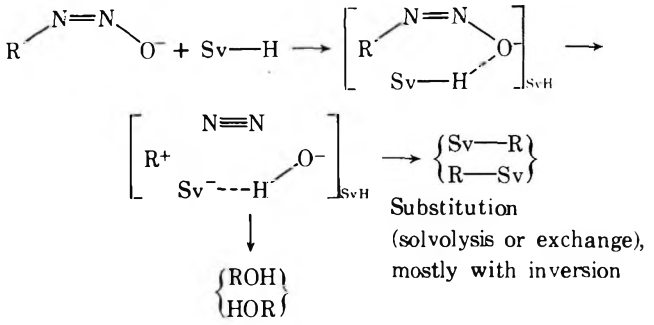
Optically active 2-aminooctane was converted to octane-2-diazotate and solvolyzed in either ethanol or thioethanol. In the ethanolysis reaction, 2-octyl ethyl ether and 2-octanol were formed with 74% overall inversion and 79% overall retention, respectively. In the thioethanolysis, 2-octyl ethyl sulfide and 2-octanol were formed with 73% overall inversion and 74% overall retention, respectively. The similarity of the results is discussed in relation to the stereochemical courses of other diazotate solvolysis reactions.

We have extensively studied the solvolysis of alkane diazotates,[3] $RN{=}NO^-$, paying particular attention to the hydrolysis,[4] ammonolysis,[5] and lithium ion catalyzed decomposition[6] of octane-2-diazotate (**1**). Scheme I has been found useful in rationalizing the results of the solvolysis reactions.[3]

Scheme I

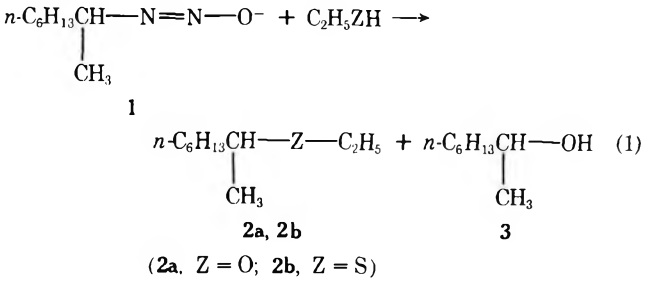


In Scheme I, Sv-H represents a protic solvent, and Sv^- represents the corresponding lyate ion. The reaction of the diazotate with a protic solvent gives the key intermediate, a nitrogen-separated ion triplet. Its collapse, by *return*, or *conservation*, affords an alcohol with net stereochemical retention, although some inverted alcohol can form if R^+ rotates within the ion triplet prior to collapse.[7] External capture of R^+ occurs mainly from the rear, affording an inverted *substitution* product, Sv-R. However, a lyate ion is hydrogen bonded to the counterion of the ion triplet, making possible a front-side collapse (*exchange*) to the stereochemically retained substitution product, R-Sv. Complete inversion in the substitution process is therefore not observed.

Upon comparison of the substitution processes in the hydrolysis[4] and ammonolysis[5] of **1**, we observed a marginally greater overall inversion in the formation of 2-aminooctane from **1** by ammonolysis (85%) in comparison with the formation of 2-octanol-^{18}O from **1** by hydrolysis with $H_2{}^{18}O$ (76%). Was this due to the greater nucleophilicity of the solvent ammonia, or was it merely a temperature effect? (The ammonolysis was carried out at −33 °C, the hydrolysis at 0 °C.) To obtain further information on the effect of solvent or lyate ion nucleophilicity in diazotate solvolyses, we have subjected **1** to ethanolysis and thioethanolysis, and determined the stereochemical courses of the substitution and return reactions in each case. The results follow.

Results and Discussion

Octane-2-diazotate[4] (13–18 mmol) was dissolved in HMPA[4a] and added to 200 ml of dry ethanol, or ethanethiol, at 0 °C. Nitrogen evolution was nearly quantitative (93–97%) in each reaction. After an aqueous work-up, the products of interest, 2-octyl ethyl ether (**2a**), 2-octyl ethyl sulfide (**2b**), and 2-octanol (**3**), were readily isolable by GC; cf. eq 1.



The yield of **2a** was remarkably constant over three ethanolysis reactions, 25 ± 1%, as determined by GC against a 2-hexanol standard. The yield of **3**, however, was relatively more variable, 2.8–3.8%, perhaps because of selective extractive loss during work-up. A reliable value of **2a/3** could therefore not be obtained. Similar problems attended the thioethanolysis experiments, in which **2b** and **3** were formed in yields comparable to those of the analogous ethanolysis products.[8] Octenes were doubtlessly formed in these reactions,[4-6] but were not examined.

Optically active 2-aminooctane was converted to **1** via its urethane and *N*-nitrosourethane derivatives,[4,9] and solvolyzed in ethanol or ethanethiol, as above. Following work-up and GC purification, the rotations of **2a**, **2b**, and **3** were polarimetrically determined. These results, and the derived *net* stereochemical courses of the reactions, are displayed

Table I. Stereochemistry of Product Formation in Solvolyses of 1

		(*S*)-(+)-*n*-$C_6H_{13}CH(CH_3)$-Z-C_2H_5			(*R*)-(−)-2-Octanol		
Run	Solvent	α^{25}D obsd, deg[a]	α^{25}D corr, deg[b]	Stereochem, %[c]	α^{25}D obsd, deg[a]	α^{25}D corr, deg[b]	Stereochem, %[d]
1	C_2H_5OH	+0.535	+7.38	48.9 net inv	−0.092	−4.76[e]	59.2 net retn
2	C_2H_5OH	+0.534	+7.36	48.8 net inv	−0.333	−4.59	57.1 net retn
3	C_2H_5SH	+0.473	+6.52	48.0 net inv	−0.262	−3.61	44.9 net retn
4	C_2H_5SH	+0.449	+6.19	45.6 net inv	−0.084	−3.98[f]	49.5 net retn

[a] Determined with a Perkin-Elmer Model 141 spectropolarimeter, using *neat*, GC-purified samples in a 0.1-dm cell. [b] Corrected for path length (to 1.0 dm), and for the optical purity of the *N*-2-octylurethane precursor from which **1** was derived. (*R*)-(−)-*N*-2-octylurethane had α^{25}D −3.25° (neat, 1 dm), corresponding to an optical purity of 72.5%.[10] [c] Optically pure 2-octyl ethyl ether has α^{22}D 15.08° (neat, 1 dm).[11] Optically pure 2-octyl ethyl sulfide has α^{25}D 13.59° (neat, 1 dm); see Experimental Section. The comparable literature value is α^{20}D 14.3°.[12] In the 2-octyl series, amine, alcohol, and ethyl ether belong to the same optical series when of the same rotational sign.[13] This must also be true of the ethyl sulfide derivative.[12] Initial (*R*)-(−)-2-aminooctane, the earliest precursor of **1**, had α^{24}D −3.80° (neat, 1 dm). These facts permit the assignment of inversion or retention to the stereochemical results listed in the table. [d] Optically pure 2-octanol has α^{23}D 8.04° (neat, 1 dm).[14] See also note *c*. [e] Product **3** was diluted with racemic **3** before determining the rotation. The dilution factor (3.75) is included in the correction. [f] Dilution factor 3.44; see note *e*.

Table II. Stereochemistry of Solvolyses of Octane-2-diazotate

			Substitution (2-Oct-X)			Return (2-Oct-OH)	
Solvent[a]	Ref	Rxn temp, °C	X	% inv	% retn	% retn	% inv
NH_3	*b*	−33	NH_2	85	15	65	35
$H_2{}^{18}O$	*c*	0	^{18}OH	76	24	73	27
C_2H_5OH	*d*	0	OC_2H_5	74	26	79	21
C_2H_5SH	*d*	0	SC_2H_5	73	27	74	26

[a] HMPA was present in all cases. [b] Reference 5. [c] Reference 4a. [d] This work.

in Table I. In Table II, we summarize the (average) overall stereochemical courses of product formation in various solvolytic reactions of **1**.

The most striking facet of Table II is the essential *invariance* of the stereochemistry of product formation observed in the hydrolysis, ethanolysis, and thioethanolysis of **1**. With reference to Scheme I, the substitution or solvolysis product is formed with 73–76% overall inversion, and the return product, 2-octanol, is formed with 73–79% overall retention of configuration, *irrespective of solvent or lyate ion identity*. This behavior further supports the postulated intermediate formation of an extremely unselective cationic 2-octyl moiety, probably as part of an ion triplet[3] (Scheme I, R^+ = 2-Oct$^+$). We have previously noted that this intermediate, when generated in a saturated aqueous solution of sodium azide, selects in a nearly statistical manner between water and azide nucleophiles,[4c,6] behavior quite at variance with that of more highly stabilized cations, which markedly prefer azide ion.[15] The sensitive stereochemical probe applied here thus affords results in agreement with the earlier observation.

Refer again to Scheme I. Ethanethiol is more acidic than ethanol,[16] so that the derived ion triplet should contain a more fully developed lyate ion in the case in which Sv^- = $C_2H_5S^-$ than in the case in which Sv^- = $C_2H_5O^-$. Moreover, the mercaptide is a stronger nucleophile than its oxygen analogue, at least when comparisons are made on scales defined by moderately reactive substrates.[19] These considerations suggest that, if the 2-octyl cation of the ion triplet were even moderately discriminating toward nucleophiles, collapse with lyate ion with front-side *exchange and stereochemical retention* would contribute to the destruction of the ion triplet more strongly when Sv = $C_2H_5S^-$ than when Sv = $C_2H_5O^-$. Accordingly, the overall stereochemistry of solvolysis product, **2**, would reflect a greater contribution from the *exchange* (retention) component in thioethanolysis than in ethanolysis; *less* overall inversion would therefore be expected in the former reaction. That this is not the case (Table II) again demonstrates the insensitivity of the ion triplet's cationic moiety to the nucleophilicity of its reaction partner.

The present results underline our previous conclusion that the nitrogen-separated ion triplet exhibits consistent and characteristic chemistry in varied reactions.[3] Small changes in the competitive blending of the pathways of Scheme I do occur, and sensibly reflect alterations of cation, nucleophile, solvent, or leaving group.[3,6] However, the hallmarks of the nitrogen-separated ion triplet's behavior appear to be its integrity and consistency, maintained despite relatively large changes in reaction parameters. This must be due to the high reactivity of its nascent cation, which ensures that subsequent reactions compete with diffusive processes, so that "selectivity" must mainly reflect the geometry of the ion triplet, particularly the relative geometry of the cation and competing nucleophiles, and that of the surrounding solvent shell.

Experimental Section

2-Aminooctane was obtained from Norse Chemical Co. and successively converted to *N*-2-octylurethane, *N*-nitroso-*N*-2-octylurethane, and octane-2-diazotate as previously described.[4] Optically active 2-aminooctane was obtained from the racemate by repeated recrystallization of its (−)-tartrate salt from methanol[20] (final mp 84–85 °C), followed by digestion of the diastereomeric salt with 6 N NaOH, extraction of the amine with ether, drying over BaO, removal of solvent, and distillation from sodium. Final purification was effected by GC, using a 5 ft × 0.25 in., 28% Pennwalt 223, 4% KOH on 80/100 Gas-Chrom R column. Samples thus purified were immediately submitted to polarimetry: α^{25}D −3.80° (neat, 1 dm). This amine was converted to (*R*)-(−)-*N*-2-octylurethane, α^{25}D −3.25° (neat, 1 dm, 72.5% optically pure[10]), with ethyl chloroformate.[4]

Solvolysis Experiments. A standard procedure is described. A slurry of 2.15 g (19.2 mmol) of potassium *tert*-butoxide in 27 ml of dry ether was prepared (under N_2) in a 250-ml three-neck flask, fitted with a low-temperature thermometer, addition funnel, gas inlet tube, and magnetic stirring bar. *N*-Nitroso-*N*-2-octylurethane (2.09 g, 9.1 mmol) in 27 ml of dry ether was slowly added, with stirring, while the reaction temperature was maintained at −30 °C. After the addition was completed, stirring was continued for 30 min at −30 °C. The reaction mixture was then allowed to warm to 20 °C, ether was removed by aspiration, and 15 ml of HMPA (Aldrich, distilled from CaH_2) was added to the residual solid to give a dark orange solution of **1**. The diazotate solution was slowly syringed into 200 ml of absolute ethanol (or ethanethiol), which was contained in a 1-l. three-neck flask, fitted with two serum caps, a gas outlet tube, and a magnetic stirring bar, and maintained at 0 °C. The solvent was vigorously stirred during the

addition of **1**. Evolved N_2 (97% of the theoretical quantity) was collected in a gas buret. After 1 h, the reaction mixture was poured into 600 ml of water and extracted with ether (5 × 50 ml), and the ethereal extracts were combined and dried ($MgSO_4$). After filtration, all low-boiling material was stripped on the rotary evaporator, and the products of interest were isolated by GC (Varian Aerograph, Model 90-P). From ethanolysis runs, **2a** and **3** were isolated using a 24 ft × 0.25 in., 10% tris(2-cyanoethoxy)propane (TCEP) on 45/60 Gas-Chrom R column (130 °C). From thioethanolysis runs, **2b** and **3** were isolated using a 18 ft × 0.25 in., 15% Carbowax 20M on 60/80 Gas-Chrom R column (150 °C). Product identities were established by comparison of ir and NMR spectra to those of authentic samples.[21] Product yields and ratios were determined from GC traces integrated with a Varian Model 481 electronic integrator. The GC thermal conductivity detector was calibrated with pure samples of products.

Stereochemical results were obtained from similar experiments, but using optically active *N*-nitroso-*N*-2-octylurethane; the relevant data appear in Table I.

2-Octyl Ethyl Sulfide. (*R*)-(−)-2-Octanol [Norse, $\alpha^{25}D$ −0.71° (neat, 0.1 dm), 88.3% optically pure[14]] was converted to the tosylate by adding 15.2 g (79.7 mmol) of freshly recrystallized *p*-toluenesulfonyl chloride to 5.00 g (38.4 mmol) of the alcohol in 75 ml of pyridine (distilled from BaO) maintained at 0 °C. The reaction mixture was kept in the refrigerator for 24 h, and the procedure described by Fieser and Fieser[22] was then used to isolate the oily tosylate, and to purify it (as a white glass at −75°).

A solution of 3.0 ml (40 mmol) of ethanethiol in 25 ml of tetrahydrofuran (THF) was treated with 30 ml of 2 N *n*-butyllithium in hexane, under nitrogen, at −65 °C. Then 7.0 g (25 mmol) of 2-octyl tosylate was added with stirring, as a solution in 25 ml of THF. The reaction temperature was kept below −40 °C. After the completion of addition, the reaction mixture was warmed to room temperature and then refluxed overnight. The product solution was poured into 200 ml of water and extracted with ether (5 × 50 ml). The combined ether extracts were dried ($MgSO_4$), filtered, and stripped of solvent. The residue was purified by GC on the TCEP column (see above) at 130 °C, to afford (*S*)-(+)-**2b**: $\alpha^{25}D$ +1.20° (neat, 0.1 dm); NMR (CCl_4) δ 2.47 (q, J = 7 Hz, SCH_2) superimposed on a *multiplet*, 2.90–2.4 (CHS), total 3 H, 1.65–1.08 (m) and 0.92 (crude t), alkyl protons, 19 H.

Correction of the observed rotation of the product 2-octyl ethyl sulfide for the optical purity of the precursor 2-octanol, and for path length, affords $\alpha^{25}D$ |13.59°| for optically pure **2b**.[12]

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Registry No.—**1**, 53475-03-9; **2a**, 36978-30-0; **2b**, 58052-40-7; **3**, 5978-70-1; (*R*)-(−)-2-aminooctane, 34566-05-7; (*R*)-(−)-*N*-2-octylurethane, 41903-73-5.

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(9) Configuration is completely retained in these conversions; cf. R. A. Moss and G. M. Love, *J. Am. Chem. Soc.*, **95**, 3070 (1973).
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Aliphatic Azoxy Compounds. III. Reduction of Nitrosoalkane Dimers as an Approach to Symmetrical Azoxyalkane Synthesis[1]

K. Grant Taylor,* Min-Shong Chi, and Melvin S. Clark, Jr.

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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Catalytic hydrogenation of nitrosoalkane dimers **3a–d** using Pd/charcoal catalyst was tested as a synthetic approach to low molecular weight, symmetrically substituted azoxyalkanes. The method appears to be useful for making *Z* azoxyalkanes of carbon content not smaller than C_4, at which point overreduction becomes a deleterious side reaction. The requisite nitrosoalkane dimers **3a–d** were preparable by peracetic acid oxidation of *E* benzaldimines (**3a–c**) or by direct oxidation of the amine (**3d**). An anhydrous work-up allowed the synthesis, by this approach, of (*E*)-nitrosomethane dimer, a more convenient procedure than those previously published. Further, mixtures of *Z* and *E* oxaziridines were obtained from the oxidation of *E* imines, a result, it is argued, which is inconsistent with a concerted, olefin-epoxidation-like mechanism. Some aspects of the NMR spectrum of azoxycyclohexane are discussed.

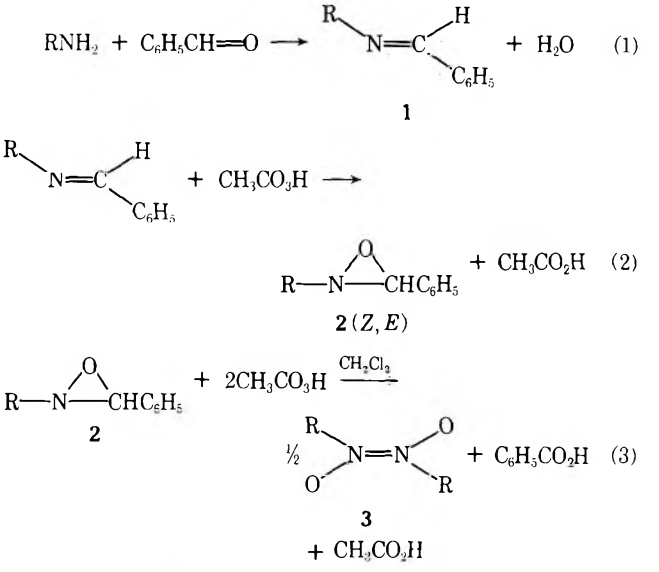
As part of a program of investigation of the chemistry of azoxyalkanes we began investigating methods of synthesis which might complement (or replace) existing synthetic approaches. A survey of the literature at the time this present project was begun indicated that the major approach to symmetrically substituted azoxyalkanes was (and still is) via oxidation of the corresponding azoalkane,[2] with the most commonly employed oxidizing agents being organic peroxy acids.[2] To complement the oxidative approach, a small selection of chemical reduction reactions was available; but these, most often involving the reduction of an aromatic nitro compound, were applicable only to the synthesis of aromatic azoxy compounds.[2] It should be noted that Snyder[3a] and Greene[3b] have recently reported the reduction of cyclic (hence, cis) azo dioxides to azoxyalkanes using hexachlorodisilane, a reagent previously employed by Mislow and co-workers in the deoxygenation of phosphine and amine oxides.[3c] The reagent will also effect the deoxygenation of cis and trans azoxyalkanes,[3a,d,e] but apparently has not been tested with acyclic nitrosoalkane dimers.[2,3f] However, Meister[4] had reported the high-yield catalytic reduction of nitrosocyclododecane and nitrosocyclohexane dimers to their respective azoxy derivatives, and this, together with Emmons' facile synthesis of nitrosoalkane dimers,[5] prompted us to test Meister's hydrogenation approach for the synthesis of lower molecular weight symmetrically substituted azoxyalkanes.[6,7] Also involved was a possible modification of Emmons' method to enable the preparation of low molecular weight nitrosoalkane dimers.

As the results below will show, atmospheric catalytic hydrogenation of nitrosoalkane dimers with palladium on charcoal catalysts is a useful method for preparation of higher molecular weight azoxyalkanes[8] but does not appear to be a worthwhile approach for the preparation of azoxyalkanes of carbon content C_4 or smaller. However, the project did yield an improved synthesis of (*E*)-nitrosomethane dimer and also afforded a key mechanistic insight into the formation of oxaziridines by the oxidation of imines with organic peroxy acids. The details are outlined below.

Results

The synthetic approach and the results are summarized below in Scheme I, reaction 4, and Table I. Regarding Scheme I, benzaldimine formation is rapid, usually exothermic, and more convenient than ketimine formation,[5] especially for low molecular weight amines. For example, for the preparation of **1a** a 40% solution of methylamine in water can be used. Only the *E* diasteromers of **1** were obtained. In reaction 2, Emmons' oxaziridine preparation, both *Z* and *E* diastereomers were obtained,[3,4] a result inconsistent with a concerted mechanism of oxidation (see below). For the preparation of nitrosoalkane dimers **3a** and **3b** it was necessary to isolate and purify (distillation) the corresponding oxaziridine. For best yields in reaction 3 some care had to be taken to keep the reagents near the stoichiometric ratio of 1 mol of **2** to 2 mol of peracetic acid. This approach resulted in the recovery of some 10–15% of unreacted oxaziridine[9] (the yields in Table I are *not* corrected for this), but employing a substantial excess of oxidizing agent gave poorer yields of nitrosoalkane dimer. The second mole of peroxy acid was required for oxidation of the benzaldehyde which is generated in the oxidation of **2**, and which competed with **2** in the consumption of peracetic acid. For the preparation of dimers **3a** and **3b** a nonaqueous modification of Emmons' work-up procedure was devised with neutralization of the acidic reaction mixture being accomplished by stirring the solution with excess powdered sodium carbonate. After solvent evaporation the (*E*)-nitrosomethane dimer present in the mixture crystallized. Washing with pentane separated it from the pentane-

Scheme I. Reaction Scheme for the Preparation of *E* Nitrosoalkane Dimers



a, R = CH_3
b, R = C_2H_5
c, R = *i*-C_3H_7
d, R = C_6H_{11}
e, R = 1-adamantyl (**3e** = 1-nitroadamantane)

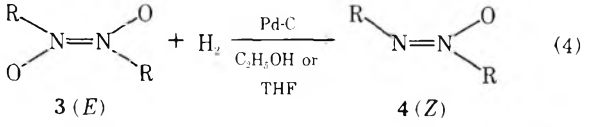
Table I. Yields (%) of Products Obtained in Scheme I and from Catalytic Hydrogenation (Reaction 4)

R	Compd: Imine, 1	Oxaziridine, 2	E nitroso dimer, 3	Z azoxyalkane, 4
CH_3	92[a]	76[b]	36	10[c]
C_2H_5	95	83[b]	50	22
i-C_3H_7	90	*d*	48	57
C_6H_{11}			36[e]	83
1-Adamantyl	90	70	*f*	

[a] Yields are of isolated products of 95–100% purity unless otherwise noted. [b] Mixture of cis and trans isomers. [c] Yield estimated from VPC. [d] Oxaziridine not isolated. [e] Dimer prepared directly from cyclohexylamine.[5] [f] 1-Nitroadamantane is the oxidation product.

soluble, unreacted (*E*)-oxaziridine. The 36% (unoptimized) yield is modest compared with the >80% obtained by periodic acid oxidation of methylhydroxylamine[10] but that procedure requires a tedious ion exchange chromatography plus lyophilization of the resulting large quantity of water. [The isolation of **3b** (R = C_2H_5) is discribed in the Experimental Section.] Not unexpectedly[5] the method failed to produce 1-nitrosoadamantane, producing, instead, the "overoxidized" product, 1-nitroadamantane (**3e**). The nitrosoalkane dimers prepared were the *E* diastereomers.

The hydrogenation reaction (4) proceeded smoothly in the case of **3d** nitrosocyclohexane dimer, in ethanol with hydrogen uptake stopping after 1.15 mol. With **3c** overreduction began to be a problem in ethanol solvent. However, with tetrahydrofuran solvent, hydrogen uptake stopped after 1.12 mol. We believe that the modest isolated yield of azoxyisopropane (**4c**) is principally a result of small-scale isolation of the liquid product (VPC yield ~80%). For nitrosoethane dimer (**3b**), overreduction was a principal cause for the low yield. Hydrogen uptake never completely stopped during the hydrogenation reaction, and the reaction was stopped after 1.3 mol uptake (6 h). For nitrosomethane dimer (**3a**), its insolubility in ethanol and THF (and other solvents) added to the problem of overreduction and a satisfactory preparation of azoxymethane was never achieved. The formation of **4a** as a reduction product was evidenced by VPC analysis.



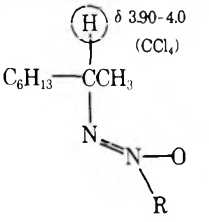
3 (*E*) 4 (*Z*) (4)

The azoxyalkanes, **4**, that were produced in reaction 4 were the known *Z* (or trans) diastereomers. For example, the azoxyisopropane produced in reaction 4 was identical with that prepared by peracid oxidation of *trans*-asoisopropane and different from that prepared by oxidation of *cis*-azoisopropane.[11] Interestingly, as indicated in Table II, in azoxycyclohexane the proximal and distal H's display an accidental magnetic equivalence, an NMR pattern strongly reminiscent of H_α's of the cyclic *E* azoxyalkanes (cis) reported by Greene[12] and Snyder.[13] In addition, the 1300-cm^{-1} ir band of the NNO function, normally a strong absorption in *Z* azoxyalkanes, was much reduced in intensity in **4d**, again reminiscent of the ir data reported for cyclic *E* azoxyalkanes.[12,13] Thus, a chemical confirmation of the geometry of azoxycyclohexane was required, and the azoxycyclohexane produced in reaction 4 was found to be identical with that produced by peroxy acid oxidation of (*E*)-azocyclohexane. Further, while the chemical shift differences for the proximal and distal H_α's ($\Delta\delta$p–d in Table II) of azoxyethane and azoxyisopropane follow the predictions of Snyder's[14] calculations and analysis, the analogous H's of azoxycyclohexane do not fit the pattern. While the chemical shift of the distal H of azoxycyclohexane appears to be "normal" if we compare it with the chemical shifts of the analogous protons of structures **5**,[15] **7**,[16] and **4c**, the chemical shift of the proximal H_α of azoxycyclohexane appears to be unusually shielded if azoxyisopropane is used as a model. However, consideration of the more appropriate model compound **6**[16] reveals that the chemical shift of the proximal H_α of azoxycyclohexane is not too far from "normal" for a cyclohexyl methine hydrogen. Further comment must await conformational analysis of acyclic azoxyalkanes.

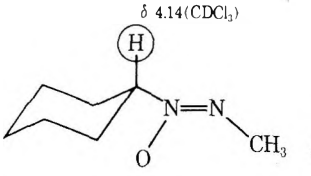
Table II. Proton NMR Chemical Shifts (δ) of Azoxyalkanes in CCl_4 Solvent

Compd	Proximal[a] H_α	Proximal[a] H_β	Distal[a] H_α	Distal[a] H_β	$\Delta\delta$ p–d for H_α
Azoxyethane	4.14 (q)[b]	1.47 (t)	3.37 (q)	1.23 (t)	0.77
Azoxyisopropane	4.38 (sp)	1.42 (d)	4.12 (sp)	1.11 (d)	0.26
Azoxycyclohexane	3.93 (m)	1.6 (bm)	3.93 (m)	1.6 (bm)	0

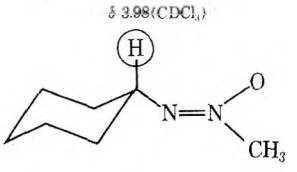
[a] Defined as follows: (proximal) HC_β–HC_α–N(O)=N–CH_α–CH_β (distal). [b] Multiplicities as follows: q = quartet (J = 6–7 Hz): t = triplet (J = 6–7 Hz); sp = septet (J = 6–7 Hz); m = multiplet (unresolved); bm = broad multiplet.



5a. R = CH_3
b. R = allyl
c. R = n-C_3H_7



6



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Observations. As mentioned above, *Z* and *E* oxaziridines, **2**, were obtained from the peracetic acid oxidation of certain *E* benzaldimines, **1**. The observed *Z*:*E* ratios and chemical shifts of the benzylic hydrogen atoms of **2** are collected in Table III. The data of Table III are consistent with those reported by Boyd[17] and co-workers for the *m*-chloroperbenzoic acid oxidation of (*E*)-*N*-alkyl-*p*-nitrobenzaldimines. Clapp and Mandan,[18] from a kinetic study of the *m*-chloroperbenzoic acid oxidation of benzaldimines, proposed a mechanism involving concerted nucleophilic displacement at peracid (dimer) oxygen by the imine CN double bond (the "olefin epoxidation" mechanism[5]). Conversely, Ogata and Sawaki,[19] from a kinetic study of the perbenzoic acid oxidation of *N*-(para-substituted benzylidene)-*tert*-butylamines, concluded that the oxidation involves two steps, proceeding, initially, by addition of peracid across the imine CN double bond, followed by ring closure to oxaziridine (the "Baeyer–Villiger type" mechanism[5]).

Table III. Relative *Z*–*E* Ratios of Oxaziridines and NMR Chemical Shifts (δ) of H_{C_3} of Oxaziridine Diastereomers in CCl_4 Solvent

R of compd 2	$\delta_{H_{C_3}}$		Ratio	
	Z	*E*	*Z*	*E*
CH_3	5.14[a]	4.37[b]	47[c]	53[c]
C_2H_5	5.12	4.35	22	78
n-C_4H_9[d]	5.06	4.28	18	82
i-C_3H_7		4.38		100
1-Adamantyl		4.90		100

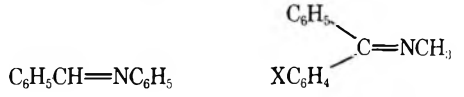
[a] δ_{CH_3} 2.22. [b] δ_{CH_3} 2.58. [c] Ratio of integration values of H_{C_3}'s. [d] Consistent elemental analysis obtained on mixture.

Table IV. Estimation of $\Delta G^{\ddagger}$ at 0°C for *Z*, *E* Isomerization of Imines

Imine	Reaction	Exp E_a, kcal	$\Delta S^{\ddagger}$, eu	Approximate $\Delta G^{\ddagger}$, 0°C, kcal mol^{-1}
8	*Z* → *E*	16.5	*a*	18
9	*Z* → *E*	25.0	−4.7	26
10	*E* → *Z*	27.1	+2.7	26
1 (R = CH_3)	*Z* → *E*			22–23[b]

[a] A $\Delta S^{\ddagger}$ range of −5 to −10 eu was used for calculation of $\Delta G^{\ddagger}$ at 0°; from k = 1.46 sec^{-1} at 30.0°,[20] $\Delta G^{\ddagger}$ = 17.5 kcal mol^{-1}. [b] Sum of $\Delta G^{\ddagger}$ at 0° for 8 plus a $\Delta\Delta G^{\ddagger}$ = 4–5 kcal; $\Delta\Delta G^{\ddagger}$ is based on a (conservative) 10^3 reduction in k for isomerization of *N*-alkylketimines compared with *N*-arylketimines.[8]

For the Clapp mechanism to be consistent with the present work two conditions must apply: (1) the rate of *E* to *Z* imine isomerization should be faster than the rate of oxidation, and (2) the rate of oxidation of *Z* imine must be faster than that of *E* imine. Regarding condition 1, from kinetic data and activation parameters published for the isomerization of imines **8**,[20] **9**,[21] and **10**,[21] a $\Delta G^{\ddagger}$ = 22–23



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9, X = *p*-Cl
10, X = *p*-NO_2

kcal mol^{-1} for *Z* to *E* isomerization of aldimines **1** can be estimated (see Table IV). To estimate $\Delta G^{\ddagger}$ for *E* to *Z* isomerization of **1**, the free-energy difference between the *Z* and *E* ($\Delta G_{Z,E}$) isomers of **1** must, again, be estimated. The value of $\Delta G_{Z,E}$ for **1** must lie between the $\Delta G_{Z,E}$ for stilbene[21] (2.3–2.9 kcal mol^{-1}, $r_{C=C}$ 1.35 Å) and the $\Delta G_{Z,E}$ for azobenzene[21] (9.9 kcal mol^{-1}, $r_{N=N}$ 1.23 Å). Using $r_{C=N}$ 1.24–1.30 Å, we estimate a $\Delta G_{Z,E}$ for **1** of 5.5–9.5 kcal mol^{-1}. This would indicate that the $\Delta G^{\ddagger}$ for *E* to *Z* isomerization of **1** at ~0°, the temperature of our oxidation conditions, could range from 27 to 31 kcal mol^{-1} (or, at the least, about 23 kcal mol^{-1}: $\Delta G^{\ddagger}$ of 8 + $\Delta G_{Z,E}$ = 5.5 kcal mol^{-1}). The activation parameters found by Clapp[18a] for the oxidation of *N*-(*p*-nitrobenzylidene)-*tert*-butylamine at 25.5° (E_a = 5.0 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −47 eu) allow an estimation of $\Delta G^{\ddagger}$ at 0°C = 18 kcal mol^{-1}. From the substantial difference between the $\Delta G^{\ddagger}$ for the *E* to *Z* isomerization of **1** and the $\Delta G^{\ddagger}$ for the oxidation reaction, one would conclude that, under usual oxidation conditions, *E* to *Z* isomerization of aldimines is decidedly slower than their oxidation to oxaziridines.[20,22] Regarding condition 2, we conservatively estimate that imine **1a** contains less than 1% of the *Z* diastereomer.[23] Given 0.1% of (*Z*)-**1a** *at equilibrium*, it would have to be oxidized 870 times faster than (*E*)-**1a** to give the ratio of isomers shown in Table III. Given the generous event of as much as 1% (*Z*)-**1a** *at equilibrium*, then (*Z*)-**1a** would have to be oxidized 87 times faster than the *E* isomer. Both of these figures seem improbably high in view of the fact that *Z* olefins are epoxidized faster than *E* olefins by a factor of only 2 or 3[25] (e.g., oleic acid:elaidic acid, 1.6; *Z*, *E* stilbenes, 1.93; (*Z*,*E*)-1,2-dineopentylethylenes, 2.6; recenoleic acid, 1.6). Thus, the fulfilling of *both* conditions required for accommodation of the present data to the "olefin epoxidation mechanism"[18] is not met. We conclude that the present stereochemical results are more consistent with, and support, the "Baeyer–Villiger mechanism" advanced by Ogata and Sawaki[19] for the oxidation of imines to oxaziridines.

Experimental Section

General. Melting points (uncorrected) were taken on a Thomas-Hoover melting point apparatus. NMR spectra were obtained on a Varian Associates A-60A spectrometer using tetramethylsilane as internal standard, and CCl_4 as solvent, unless noted otherwise. Ir spectra were obtained on a Perkin-Elmer 337 (grating) spectrometer and uv spectra with a Cary 14 spectrophotometer. Midwest Microlab, Inc., Indianapolis, Ind., performed the elemental analyses. Analyses by VPC were performed on Hewlett-Packard instruments: Model 5750 with flame ionization detector or Model 700 with a thermal conductivity detector. The following columns were used: column A, 15% Carbowax 20M on Anakrom; column B, 10% Hewlett-Packard silicone rubber UCW 98 on Chromosorb G (NAW); column C, 2% silicone rubber UCW-98 on Diatoport S.

Preparation of Imines. Two procedures were used. (A) For water-soluble amines, e.g., methylamine, equal volumes of ether and 40% aqueous methylamine were stirred and cooled to 0°. Benzaldehyde (limiting reagent) was then added dropwise to the stirred mixture, and, after addition was complete, the cooling bath was removed and stirring continued for 2 h. Solid NaOH was then added, the organic layer separated and dried (Na_2CO_3 or NaOH), and the product isolated by distillation in vacuo from a few KOH pellets. (B) For water-insoluble amines, the amine was cooled to 0° and, with stirring, an equivalent amount of benzaldehyde was added dropwise. After completion of the addition, cooling was discontinued and stirring continued for 1 h. Solid NaOH was then added, at which point the procedures became identical.

***N*-(Benzylidene)methylamine (1a),**[26] procedure A: bp 89° (30 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.15 (methine H).

***N*-(Benzylidene)ethylamine (1b),**[26] procedure A: bp 109° (47 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.17 (methine H).

***N*-(Benzylidene)-2-propylamine (1c),**[26] procedure B: bp 116° (24 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.34 (methine H).

***N*-(Benzylidene)-1-butylamine,** procedure B: bp 56–57° (0.03 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.32 (methine H).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.39; N, 8.69. Found: C, 81.93; H, 9.53; N, 8.93.

***N*-(Benzylidene)-1-adamantylamine (1e),** procedure B (inverse addition): mp 58–61°; ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.20 (methine H).

Anal. Calcd for $C_{17}H_{21}N$: C, 85.31; H, 8.84; N, 5.85. Found: C, 85.24; H, 8.91; N, 5.83.

Preparation of Oxaziridines. The method of Emmons[5] was used.

2-Methyl-3-phenyloxaziridine (2a):[26] bp 64° (0.27 mm); NMR δ 6.97 (s, phenyl H).

2-Ethyl-3-phenyloxaziridine (2b):[26] bp 42° (0.1 mm); NMR δ 7.3 (two singlets with 0.8-Hz separation, *Z*, *E* phenyls), 2.81 (q, J = 7 Hz, *E*-CH_2), 2.58 (q, J = 7 Hz, *Z*-CH_2), 1.17 (t, J = 7 Hz, *E*-CH_3), 0.99 (t, J = 7 Hz, *Z*-CH_3).

(*E*)-2-(2-Propyl)-3-phenyloxaziridine:[26] bp 52° (0.05 mm); NMR δ 7.31 (d, phenyl H), 2.21 [septet, J = 6.5 Hz, $HC(Me)_2$], 1.21, 1.04 (two doublets, J = 6.5 Hz, nonequivalent isopropyl group CH_3's).

(*Z*,*E*)-2-(1-Butyl)-3-phenyloxaziridine: bp 72–76° (0.09 mm); NMR, see Table III; complex patterns seen for butyl group signals.

Anal of mixture. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.71; H, 8.76; N, 8.09.

(*E*)-2-(1-Adamantyl)-3-phenyloxaziridine (2e): mp 69–72°; NMR, see Table III.

Anal. Cacld for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.20; H, 8.38; N, 5.41.

(*E*)-Nitrosomethane Dimer (3a). Anhydrous peracetic acid[5,27]

(1.02 mol) in 120 ml of methylene chloride was added dropwise to an ice-cooled solution of 61.6 g (0.45 mol) of **2a** in 120 ml of methylene chloride. The mixture was allowed to gradually warm to room temperature (with stirring) over a 12-h period. After further dilution with methylene chloride the solution was stirred with excess powdered anhydrous sodium carbonate until carbon dioxide evolution ceased. After filtration, the solvent was evaporated in vacuo at room temperature, affording a pale yellow solid plus a pale yellow liquid. Dissolution of the liquid in pentane yielded (as residue) 7.31 g (36%) of white, crystalline **3a**, mp 120–122° (lit.[28] mp 122°), NMR ($CDCl_3$) δ 3.89 (s) [lit.[29] δ 4.0 (s)]. Distillation of the pentane wash afforded recovery of 8.25 g (13%) of (*E*)-**2a**.

(*E*)-Nitrosoethane Dimer (3b). Anhydrous peracetic[27] acid (0.86 mol) in 120 ml of methylene chloride was used to oxidize 52.6 g (0.35 mol) of **2b** using the procedure successful for the preparation of **3a**. After filtration of the sodium carbonate (neutralizing and drying agent), evaporation of the solvent failed to produce a crystalline residue. Thus the liquid residue was distilled at room temperature in vacuo. The distillate, bp 22° (0.15 mm, collected in a receiver cooled to −78°), was further purified by recrystallization from ether at −78°. Siphoning of the ether solvent [from which 4.5 g (8.5%) of (*E*)-**2b** was recovered] gave 10.6 g (50%) of (*E*)-nitrosoethane dimer, a liquid at room temperature: uv (H_2O) λ_{max} 277 nm (lit.[28,30] λ_{max} 277 nm); NMR δ 4.00 (q, J = 7 Hz, CH_2), 1.30 (t, J = 7 Hz, CH_3); mass spectrum *m/e* (rel intensity) 118 $M^{\cdot+}$ dimer (~1), 117 $M^{\cdot+}$ dimer − H (~1), 71 (5), 59 $M^{\cdot+}$ nitrosoethane monomer (65), 41 *m/e* 71 − NO (74), 30 $M^{\cdot+}$ monomer − C_2H_5 (35), 29 $M^{\cdot+}$ monomer − NO (56), 27 HCN (100); metastables at 23.7 and 14.25 support the *m/e* 71 − NO and 59 − NO fragmentations, respectively.

Anal. Calcd for $C_4H_{10}N_2O_2$: C, 40.66; H, 8.53; N, 23.72. Found: C, 40.92; H, 9.19; N, 23.74.

(*E*)-2-Nitrosopropane Dimer (3c). Anhydrous peracetic acid[27] (1.2 mol) in 150 ml of methylene chloride was added dropwise to an ice-cooled solution of 53.3 g (0.36 mol) of imine **1c** in 100 ml of methylene chloride. After addition, the stirred mixture was allowed to warm to room temperature and remain as such overnight. The mixture was then washed successively with dilute aqueous sodium sulfite solution, water, and dilute aqueous sodium bicarbonate solution. The organic layer was then dried (sodium carbonate) and evaporated in vacuo. The resulting oily residue was dissolved in 60 ml of ether and cooled at −78° for 0.5 h. Filtration gave 12.8 g (48%) of colorless, crystalline **3c:** mp 51–52° (lit.[5] mp 53°); NMR δ 5.43 [septet, J = 6.5 Hz, $HC(Me)_2$], 1.35 (d, J = 6.5 Hz, *gem*-dimethyl groups). From the filtrate 5.5 g (~9%) of (*E*)-**2c** was recovered by distillation in vacuo.

(*E*)-Nitrosocyclohexane Dimer (3d). Cyclohexylamine was oxidized as previously described[5] to give **3d** in 36% yield: mp 118° (lit.[5] mp 119–120°); NMR δ 5.17 (broad m, HCNO), 1.9 (broad m, ring CH_2).

(*Z*)-Dicyclohexyldiazene Oxide (4d). A solution of 1.0 g (0.004 mol) of 3d in 10 ml of ethanol was hydrogenated at 1 atm using 50 mg of 5% or 10% palladium on charcoal. Hydrogen uptake ceased after 3.5 h and 1.15 mol consumption. Filtration and evaporation of the solvent gave a residue which, on short-path distillation (in vacuo), gave 0.77 g (83%) of colorless **4d:** mp 20–22° (lit.[4] mp 22°); ir (neat) 1493 (s), 1290 cm^{-1} (w) (lit.[31] ir 1495 and 1285 cm^{-1}); VPC (column B, 6 ft × 0.125 in.) indicated 98% purity; *m*-chloroperbenzoic acid oxidation of azocyclohexane[31] gave **4d**, identical with that obtained by hydrogeneration of **3d**.

(*Z*)-Bis(1-methylethyl)diazene Oxide (4c). In a manner similar to that for **3d**, 1.16 g (0.008 mol) of **3c** in 5.3 ml of THF was hydrogenated using 43 mg of palladium on charcoal. Hydrogen consumption was 1.12 mol in 9.5 h. Filtration and evaporation of the solvent gave a residue which was dissolved in methylene chloride and passed over a 15-g column of alumina. The first 15 ml of eluent was collected and distilled (1 atm) to give 0.60 g (57%) of colorless **4c:** VPC (column C, 6 ft × 0.125 in.) indicated 96% purity; bp 134–135° [lit.[31] bp 38° (14 mm)]; ir (neat) 1500 (s) and 1297 cm^{-1} (s) (lit.[31] ir 1500 and 1295 cm^{-1}).

(*Z*)-Diethyldiazene Oxide[8b] (4b). A tetrahydrofuran solution of **3b** (1.38 g, 0.012 mol) was hydrogenated using 67 mg of Pd/charcoal. The reaction was discontinued after 1.3 mol of hydrogen was consumed. The THF solvent was distilled at atmospheric pressure and the product, **4b**, was isolated by preparative VPC (column A, 6 ft × 0.25 in.) of the distillation residue. The yield of pure **4b** was 0.265 g (22%): ir (neat) 1510 (s) and 1318 cm^{-1} (s); NMR, see Table II.

Caution. Azoxyethane is a demonstrated carcinogen in experimental animals.[7] Isolation procedures should be conducted with appropriate ventilation and trapping of contaminated effluents.

Hydrogenation of (*E*)-Nitrosomethane Dimer. Attempts to prepare **4a** were made using both Pd/charcoal and PtO_2 catalysts in methanol, ethanol, and THF. Overreduction was a problem in all three solvents, and azoxymethane was observed to codistill with all three solvents. Azoxymethane was seen to be a reduction product by VPC identification using an authentic sample.[32] With Lindlar catalyst, no hydrogen uptake was observed.

Oxidation of Adamantyl Derivatives. Peracetic acid oxidation of both 1-adamantylamine and oxaziridine **2e** gave 1-nitroadamantane as the major product (40–60%), mp 155° (lit.[33] mp 158°).

Registry No.—**1a**, 25521-74-8; **1b**, 27845-47-2; **1c**, 27845-51-8; **1e**, 57527-54-5; **1** (R = *n*-C_4H_9), 57527-55-6; *cis*-**2a**, 39245-63-1; *trans*-**2a**, 40264-03-7; *cis*-**2b**, 57527-56-7; *trans*-**2b**, 57527-57-8; *trans*-**2c**, 57527-58-9; *trans*-**2e**, 57527-59-0; *cis*-**2** (R = *n*-C_4H_9), 57527-60-3; *trans*-**2** (R = *n*-C_4H_9), 57527-61-4; **3a**, 37765-15-4; **3b**, 57527-62-5; **3c**, 57527-63-6; **3d**, 26049-06-9; **4b**, 57527-64-7; **4c**, 35216-94-5; **4d**, 57497-40-2; benzaldehyde, 100-52-7; methylamine, 74-89-5; ethylamine, 75-04-7; isopropylamine, 75-31-0; *n*-butylamine, 109-73-9; 1-adamantylamine, 768-94-5; cyclohexylamine, 108-91-8.

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(23) (a) We examined the NMR of **1a** in detail, especially the region upfield from NCH_3,[24] in "normal" NMR solvents and also under conditions mimicking our oxidation conditions (acetic acid added, trace H_2SO_4, peracid omitted). By spiking with a known quantity of a CH_3 standard we concluded that 1% of (*Z*)-**1a** would have been readily detected in the NCH_3 region. (b) Karabatsos and Lande list the *E/Z* ratio of 14 aldi-

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Aliphatic Azoxy Compounds. IV. Reaction of Nitrosoalkanes with Hydroxylamines. Synthesis of Unsymmetrical Primary and Secondary Azoxyalkanes by N–N Bond Formation[1]

K. Grant Taylor,* S. Ramdas Isaac, and Melvin S. Clark, Jr.

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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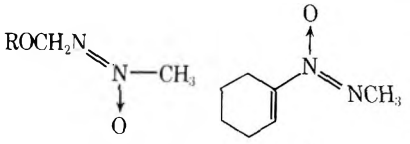
The condensation of *N*-alkylhydroxylamines with photolytically monomerized nitrosoalkanes yields mixtures of O-position isomers of *Z* azoxyalkanes **5a–g** and **6c–g** in ~30–95% yields. The major isomer is that one with the less bulky N substituent syn to the oxygen atom of the azoxy group. This isomer predominates regardless of whether the less bulky group is on the hydroxylamine or nitrosoalkane reactant. Use of *N*-alkyl-*O*-methylhydroxylamines in the condensation gives a single azoxyalkane product, that isomer wherein the azoxy oxygen atom is derived from the nitrosoalkane; however, the yields are low in these reactions. Aspects of the uv and NMR spectra of the azoxyalkanes are discussed.

Aliphatic[2] and aromatic[3] azoxy compounds exist in nature and, without exception, are unsymmetrically substituted compounds with potent physiological activity. An example of recent interest is cycasin (**1a**), known to be carcinogenic in experimental animals.[2d] The aglycone of cycas-



1a, R = D-glucosyl
b, R = H
c, R = $COCH_3$

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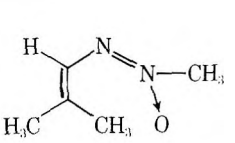

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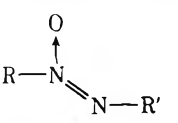
in, **1b**, the synthetic acetate, **1c**, and synthetic low molecular weight azoxyalkanes are among the most potent of chemical carcinogens.[2d,4] There has been a sustained interest in the chemistry of azoxyalkanes, but, as Moss[5] has pointed out, until 1972 there existed no general, directed method for the synthesis of unsymmetrically substituted azoxyalkanes. The major approach to the synthesis of such compounds has been the oxidation of unsymmetrical azoalkanes,[6] and, to date, no clear mechanistic picture has emerged to permit a prediction of which NO-position isomer can be expected as the major product of oxidation. For example, **2** and **3** are the azoxy compounds isolated from oxidations of the respective azoalkenes.[7] In the aromatic series, all nonortho substituents on monosubstituted diaryldiazenes seem to mildly direct the oxidation toward the more remote N atom of the azo linkage.[8] Moss and co-workers' alkylation of alkane diazotates[5] of structure R′–N=N–O⁻ by alkyl iodides, RI, gives *Z* azoxyalkanes **4** in 32–64% yields. The reaction, a C–N bond synthesis via SN2 displacement,[5b] is best suited for the preparation of **4** when R is a primary alkyl group and R′ is either a primary or secondary alkyl group. When R is a secondary alkyl group the yield of azoxyalkane is decreased (competing E2?), as it also is when R′ is a tertiary alkyl group of an alkane diazotate (competing O-alkylation?).[5] Kovacic and co-workers[9] have also developed a directed synthesis of azoxyalkanes. Based on N–N bond formation between nitroso compounds and *N,N*-dichloroamines, the approach is applicable to the synthesis of unsymmetrical tertiary dialkyldiazene monoxides.

Our attention was drawn to the N–N bond formation approach by the work of Freeman,[10] who, in extending Aston's[11] work, reported the formation of (for practical purposes) only **5a** and **5b** from the condensation of *N*-methylhydroxylamine with nitrosobenzene and 2-methyl-2-nitrosopropane, respectively. These results stood in sharp contrast to the results of such condensations in the aromatic series. For example, the condensation of *p*-chloronitrosobenzene with phenylhydroxylamine gives azoxybenzene and 4,4′-dichloroazoxybenzene in addition to an unsymmetrical azoxyarene.[12] Work by Russell and Geels[13] substantiated an oxidation–reduction pathway (eq 1) for the for-

$$\mathrm{ArNO} + \mathrm{ArNHOH} \longrightarrow [\mathrm{ArNHO}\cdot] \longrightarrow \mathrm{ArN(O){=}NAr} \quad (1)$$



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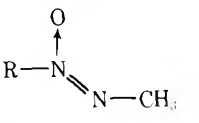
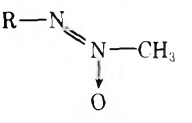


5a, R = C_6H_5
b, R = t-C_4H_9
c, R = C_2H_5
d, R = C_6H_{11}
e, R = $C_6H_5CH_2$
f, R = $C_6H_5CHCH_3$
g, R = o-$CH_3C_6H_4$



6a, R = C_6H_5
b, R = t-C_4H_9
c, R = C_2H_5
d, R = C_6H_{11}
e, R = $C_6H_5CH_2$
f, R = $C_6H_5CHCH_3$
g, R = o-$CH_3C_6H_4$

Table I. Yields of Unsymmetrical Azoxy Compounds from the Condensation of $(RNO)_2$ with R'NHOH at pH 6–7

Entry	R[i]	R'[j]	Conditions: Solvent,[a] λ[b] (temp, °C)	Yields[c]: % 5	% 6	Total	Ratio 5/6
1	C_6H_5	CH_3	A, dark (0)	69	Trace	69	25–30
2	t-C_4H_9	CH_3	A, dark (38)	52	1	53	25–30
3	CH_3	t-C_4H_9	B, 300 (45)	7[d]		7[d]	25–30
4	C_2H_5	CH_3	B, dark (25)			Low	2[e]
5	C_6H_{11}	CH_3	B, 350 (10)			83	11
6	C_6H_{11}	CH_3	B, dark (65)			84[f]	5[f]
7	C_6H_{11}	CH_3	C, dark (65)	63	16	95[g]	2.7[d]
8	CH_3	C_6H_{11}	B, 300 (45)	38.5[f]	5.9[f]	44.4[f]	6.5
9	$C_6H_5CH_2$	CH_3	D, 300 (45)	39.3[f]	16[d]	55	2.5[d]
10	$C_6H_5CHCH_3$	CH_3	D, 350 (10)	63.7[f]	16[d]	80	3.9[d]
11	$C_6H_5CHCH_3$	CH_3	D, dark (65)	41[f]	18[d]	59	2.3[d]
12	o-$C_6H_4CH_3$	CH_3	E, dark (0)	60[d]	7[d,h]	67[d]	8.5

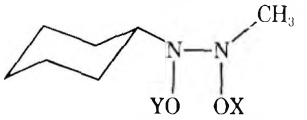
[a] Solvent A: THF–H_2O, 2:1 by volume; B: methanol; C: THF–methanol, 9:1 by volume; D: methanol–H_2O, 9:1 by volume; E: THF–H_2O, 9:1 by volume. [b] λ is the principal emission wavelength (nm) of the Rayonet RPR 100 photochemical reactor lamp used. [c] Yields are of isolated, pure products unless noted otherwise. [d] Determined by NMR analysis of the reaction mixture using an internal standard. [e] Yield was not determined; ratio was estimated by VPC analysis. [f] Determined by VPC analysis using an internal standard. [g] Yield includes a distillation fraction of a mixture of **5** and **6**. [h] Compound 6g was isolated in small amount by preparative VPC. [i] Registry no. for respective compounds are 586-96-9, 6841-96-9, 14523-95-6, 57497-47-9, 13000-13-0, 26779-46-4, 30285-71-3, 611-23-4. [j] Registry no. for respective compounds are 4229-44-1, 57497-39-9, 25100-12-3.

mation of the symmetrical azoxybenzenes in such reactions. Thus, on the surface, the results of Freeman,[10] wherein the azoxy compound's oxygen atom was derived from the nitroso compound, gave indication that the condensation of nitrosoalkanes with *N*-alkyl hydroxylamines might provide a directed synthesis of unsymmetrical azoxyalkanes. We, accordingly, investigated this possibility and the results are outlined below.

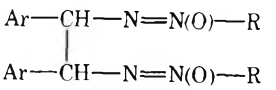
Results

The reaction conditions (basic, refluxing ethanol) employed by Freeman[10] for the preparation of **5a** and **5b** appeared to be too strong for general applicability, because of the sensitivity of nontertiary nitrosoalkanes toward base-catalyzed rearrangement to the corresponding oxime isomers.[14] Also, in our hands, repetition of Freeman's synthesis of **5a** produced azoxybenzene as the major product (70%), a synthesis more easily accomplished by mixing only nitrosobenzene with alcoholic sodium hydroxide.[15] We found that the reaction of nitrosobenzene with *N*-methylhydroxylamine at 0° in THF–H_2O, buffered with *N*-methylhydroxylamine hydrochloride at the start[16] to pH 6.8, gave consistent yields of **5a** *near* 69% with the yield of azoxybenzene reduced to 10–15% (see Table I, entry 1). The same conditions were applied successfully to the preparation of, first, the *o*-tolyl homologue, **5g** (Table I, entry 12), and secondly, by using a convenient temperature for the dissociation of 2-methyl-2-nitrosopropane dimer, to a somewhat improved preparation of **5b** (Table I, entry 2). In the syntheses of **5a** and **5b**, NMR spectral absorptions and VPC peaks attributable to the isomeric compounds **6a** and **6b** indicated that 3% or less of these isomers were formed in the reactions. In contrast, the reaction leading to **5g** gave a **5g/6g** ratio of 8.5, enough **6g** to permit isolation and characterization.

However, nitrosobenzene is monomeric and tertiary nitrosoalkane dimers are readily dissociated to monomers without the possibility of isomerization to the oxime. In contrast, merely permitting nitrosoethane dimer to dissociate at room temperature in the presence of *N*-methylhydroxylamine (pH 7–8) gave azoxyalkanes **5c** and **6c**, but the reaction time was too long (3 days) and the yields unsatisfactorily low with several by-products formed (Table I, entry 4).[17] In a similar vein, little or no reaction occurs between nitrosocyclohexane dimer and *N*-methylhydroxylamine at or below room temperature. However, as DeBoer demonstrated,[18] it is possible to dissociate nitrosoalkane dimers by photolysis without incurring dissociation of the resulting monomer into R· and NO. Accordingly, the reaction of nitrosocyclohexane dimer with *N*-methylhydroxylamine in buffered methanol at 10° gives an 83% isolated yield of a mixture of **5d** and **6d** if the reaction is irradiated with a medium- or high-pressure uv light source (Table I, entry 5). Although a mixture was obtained, the favorable ratio of **5d/6d** of 11 prompted us to test the alternate condensation of nitrosomethane dimer with *N*-cyclohexylhydroxylamine. As entry 8 of Table I records, however, **5d** was again the major azoxy isomer produced in a rather favorable ratio but in lower yield. In a like manner, *tert*-butylhydroxylamine reacted with nitrosomethane dimer to produce only **5b** in very low yield (Table I, entry 3). Close examination of the reactions described as entries 2, 3, 5, and 8 (particularly 5, 8, and others of the "cyclohexylmethyl" series, 6 and 7) revealed that the symmetrical azoxyalkanes were not formed in these reactions, a result which, in our thinking, ruled out an oxidation–reduction pathway (eq 1) as being responsible for the formation of the mixture of azoxyalkane isomers. Rather, we speculated that the formation of the **5d–6d** mixture resulted from the partitioning of an *N,N'*-diol intermediate, such as **7a** or



7a, X = Y = H
b, X = CH_3; Y = H
c, X = H; Y = CH_3



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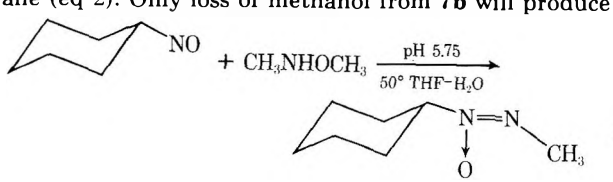
some reactive equivalent, in a final dehydration step which yields the azoxyalkanes.[19] Accordingly, we "synthesized" intermediate **7b** by the condensation of *N,O*-dimethylhydroxylamine with thermally monomerized nitrosocyclohexane (eq 2). Only loss of methanol from **7b** will produce an



(2)

5d

azoxyalkane, and only azoxyalkane **5d** was produced in this reaction (55%). Also, we "synthesized" intermediate **7c** by the condensation of *N*-cyclohexyl-*O*-methylhydroxylamine with photolytically monomerized nitrosomethane, and this time only **6d** was formed (16%). Thus, reaction 2 and its counterpart just mentioned represent directed syntheses of unsymmetrical azoxyalkanes. It should be pointed out, however, that the yield of reaction 2 is an optimized yield. *N,O*-Dimethylhydroxylamine (pK'_a = 4.75) is more sluggish than *N*-methylhydroxylamine (pK'_a = 5.97) in its reaction with nitrosobenzene (little **5a** after 14 h at 0°), and the similar lowering of reactivity toward nitrosocyclohexane requires a prolonged irradiation of the photolytically aided condensation which leads in turn to an increase in photochemical side reactions. Also, the low yield of **6d** from the *N,O*-dialkylhydroxylamine route was not a promising sign.

Thus, while that condensation which uses *N*-alkylhydroxylamines gives azoxyalkane mixtures, the yields can be quite high and the azoxyalkane isomers are separable by standard techniques. As entries **6** and **7** of Table I illustrate, thermal dissociation of nitrosoalkane dimers in this synthesis is also feasible. The nitrosoalkane monomer, though it condenses with the alkylhydroxylamine, does tautomerize to the corresponding (unreactive) oxime during these condensations. Thus, cyclohexanone oxime was detected (5–10% by VPC) in the reaction mixtures of entries 5–7 of Table I as was benzaldehyde oxime (entry 9) and acetophenone oxime (entries 10 and 11). The benzylic-type nitrosoalkane dimers of entries 9–11 of Table I were chosen, in part, to provide a test of the method with easily tautomerized and photolytically cleaved nitrosoalkane monomers. The method gives satisfactory yields of azoxyalkanes, and entries 10 and 11 allow a comparison of the thermal and photolytic methods for the monomerization of easily tautomerized nitrosoalkanes. It should be noted that azoxyalkane **6e** was not completely characterized but could be reproducibly detected by NMR analysis of freshly extracted reaction mixture [δ 4.05 (broadened, singlet, CH_3NO), 4.57 (narrow quartet, $-CH_2N=$)]. The compound was somewhat unstable, presumably owing to a facile oxidative dimerization which has been known to yield compounds of type 8 in similar structural situations.[20]

In every case recorded in Table I, isomer **5** is the major product. Were electronic factors dominant such that the dehydrative partitioning of **7a** placed the more electron-releasing R group on the formally (+) charged oxidized nitrogen atom (e.g., $\sigma^*_{t\text{-}C_4H_9}$ −0.30, $\sigma^*_{CH_3}$ 0.00), then for the **5e–6e** and **5f–6f** isomer pairs, one would predict that the **6** isomers should predominate, since the benzyl group (σ^* +0.215) and the α-phenylethyl group (σ^* ~+0.10) are electron withdrawing relative to CH_3. Thus, steric factors dominate in the partitioning of **7a** such that the major final product has the less bulky CH_3 group (in general, that group with the higher Taft E_s value[21]) located syn to the oxygen atom.

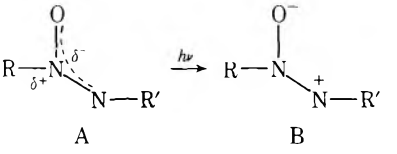
In summary of the above, the condensation of *N*-alkylhydroxylamines and nitrosoalkanes would appear to be useful for the good-yield preparation of unsymmetrical azoxyalkanes **4**, wherein R is a secondary or tertiary alkyl group and R′ is methyl or a primary or secondary alkyl group. While our interests led us to prepare examples of azoxyalkanes all of which contained an *N*-methyl group, there are isolated examples of symmetrical secondary[6,22] and tertiary[6,23] azoxyalkanes having been synthesized by N–N bond formation such that we feel the above general statement of utility is justified.

Uv Spectra. The uv spectra of azoxyalkanes **5b, 6b,** and **5d** and **6d** had uv maxima in the expected range for *Z* azoxyalkanes [λ_{max} 215–224 nm (ϵ ~7000), infl at 270–280 nm (ϵ ~500)]. The work of Jaffé and co-workers has indicated that upon electronic excitation, the azoxy function of azoxybenzenes shows a substantial increase in basicity[24a] [e.g., for $C_6H_5N(O)=NC_6H_5$, ground-state pK_a = −6.57, excited state pK'_1 = 3.23]. Since the initial site of protonation of ground-state azoxybenzene is the azoxy oxygen atom,[24b] it would seem that in the excited state that atom experiences a substantial increase in electron density, and, later work by Jaffé lends strong support to this supposition.[24c] In azoxybenzenes, the increase in electron density at oxygen can come at the expense of the aromatic π system and its substituents. In azoxyalkanes, such an increase in electron density at the O terminus must be compensated for by a loss of electron density principally from the N terminus and, to what extent is possible, from the N-terminus substituent. (See structures A and B.) As the data of Table II show (with but single exception), it is R′ which influences the position of the principal λ_{max} of azoxyalkanes, with the better electron-donating substituents (those with a lower Taft σ^* or σ_I) moving the λ_{max} toward longer wavelength. Thus, when R′ is CH_3 or primary alkyl, λ_{max} = 216 ± 2 nm; when R′ is secondary or tertiary alkyl, λ_{max} = 222 ± 2 nm.

Table II. Uv Absorption Maxima of Representative Azoxyalkanes, RN(O)=N–R′

Structure		
R	R′	λ_{max}, nm
CH_3	CH_3	217[a]
n-C_3H_7	n-C_3H_7	217[a]
n-C_4H_9	n-C_4H_9	218[b]
i-C_3H_7	i-C_3H_7	220.5[a]
Cyclohexyl[f]	Cyclohexyl	224[c]
t-C_4H_9	t-C_4H_9	221[b]
t-C_8H_{17}	t-C_8H_{17}	223[a]
C_2H_5	n-C_8H_{17}	217.5[d]
C_2H_5	sec-C_8H_{17}	221.5[d]
CH_3	Cyclohexyl	222[c]
C_2H_5	t-C_8H_{17}	224[d]
Cyclohexyl	CH_3	214[c]
sec-C_4H_9	n-C_8H_{17}	222.5[d,e]
t-C_4H_9	CH_3	215[c]

[a] Reference 25. [b] Reference 26. [c] This work. [d] Reference 5. [e] The exception to the rule; see text. [f] Registry no., 57497-40-2.

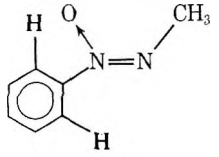


A B

The uv spectra of the aryl compounds **5a, 6a**,[27] **5g,** and **6g** indicate that the aryl ring of **5g** is twisted from coplanarity with the azoxy function. Thus, the spectrum of **5a**[27] is similar to that of nitrobenzene. Compound **6a**,[27] with its intense absorption at 288 nm, reflects the effect of extended conjugation in this isomer. By contrast, the spectrum of **5g** is more similar to that of a nonaryl azoxy compound with a principal maximum (ϵ 7700) in the range of the compounds listed in Table II, and only a modest maximum at 264 nm (ϵ 1100) (phenyl B band?). The spectrum of **6g** (Chart I) is normal and consistent with coplanar aryl and azoxy groups (compare **6a,** Chart I). For **5g,** in a completely planar conformation, the ortho methyl group would interact strongly with either the oxygen or the NCH_3 portions of the azoxy group.

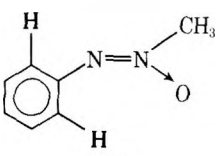
With the benzyl-type compounds **5e, 5f,** and **6f,** the azoxy group absorption was masked by the intense benzene-ring "end absorption"[28] (ϵ ~10^4 at 220 nm).

Chart I. Principal Uv Maxima (nm) and Ortho Proton Chemical Shifts of Aryl–Alkyl Azoxy Compounds



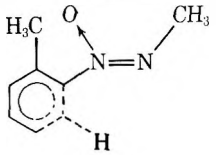
δ 8.17

5a, λ_{max} 245



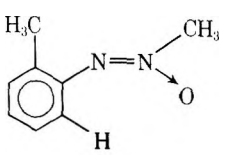
δ 7.87

6b, λ_{max} 228, 288



δ 7.50

5g, λ_{max} 223



δ 7.60

6g, λ_{max} 228, 294

NMR Spectra. The NMR chemical shifts of the α H's of azoxyalkanes are, by and large, unpredictable. Recent theoretical efforts by Snyder[29] have given some rationale to the observed nuances but problems remain.[1b] Table III records

Table III. Proton NMR Chemical Shifts (δ) of Azoxyalkanes in $CDCl_3$ Solvent

Compd	Proximal H_α[a]	Distal H_α[a]	H_β (other)
5b		3.12 s[b]	1.50 s proximal
6b	3.96 s		1.25 s distal
5c	3.98 q[c]	2.94 s	1.39 t[c] proximal
6c	3.99 t[d]	3.37 q[c]	1.23 t[c] distal
5d	4.14 m	3.10 s	
6d	4.02 s	3.98 m	
5e	5.25 s	3.15 s	7.33 bs (C_6H_5)
6e[e]	4.05 bs	4.57 q[d]	7.36 bs (C_6H_5)
5f	5.50 q[c]	3.20 s	1.83 d[c] proximal
6f	4.05 s	5.15 q[c]	1.47 d[c] distal
5g		3.40 s	2.34 (o-$C_6H_4CH_3$)
6g	4.23 s		2.22 (o-$C_6H_4CH_3$)

[a] Defined as follows: proximal-HC_β–HC_α–N(O)=N–C_αH–C_βH-distal. [b] s = singlet; bs = broadened singlet; m = multiplet; t = triplet; d = doublet; q = quartet. [c] $J \simeq 7$ Hz. [d] J = 1–1.5 Hz. [e] Signals observed in a mixture of **5e**, **6e**, and benzaldehyde oxime, and also in a small sample of **6e** separated by chromatography.

the chemical shifts of the proximal and distal[30] α H's of the azoxy compounds prepared in this work. Features of the NMR spectra (see Chart I) of aryl compounds **5a**,[27] **6a**,[27] **5g**, and **6g** are consistent with a noncoplanar aryl ring and azoxy group in **5g** as was deduced earlier from the uv data. Thus, the ortho aryl proton of **5g** is shielded by almost 0.7 ppm relative to the ortho protons of **5a** (see Chart I). By contrast, the ortho proton of **6g** has a more "normal" chemical shift (compare **6a**). Similar shielding of ortho protons was observed for the *E* diastereomers of **5a** and **6a**.[27] Tilting of the aryl ring out of copolanarity with the azoxy function apparently moves the ortho proton to a location of relative long-range shielding above the plane of the azoxy group.[31] The ortho CH_3 group might be expected to experience this same effect, but at present no unequivocal model for comparison is available.

Experimental Section

General. NMR spectra were obtained with a Varian A-60A spectrometer using tetramethylsilane as internal standard. Infrared spectra were obtained on Perkin-Elmer 337 or Beckman IR-12 spectrophotometers. Uv spectra were obtained on a Cary 14 spectrophotometer in 95% ethanol solutions. Midwest Microlab, Inc., Indianapolis, Ind., performed the elemental analyses. VPC analyses were conducted on Hewlett-Packard 5750 (flame detector) and 700 (thermal conductivity detector) instruments.

For VPC analyses the following columns were used: A, 5% Carbowax 20M on Anakrom or Chromosorb W (AW and DMCS); B, 5% UCW-98 on Diatoport S; C, 10–20% Carbowax 20M on Chromosorb W (AW and DMCS); D, 20% SE-30 on Anakrom.

Photochemical reactions were performed in a nitrogen atmosphere using either a medium-pressure 450-W Hanovia type L lamp (lamp H) or, more often, with a Rayonet photochemical reactor, Model RPR-100 (lamp R) equipped with a 16-tube, variable light source with 350 or 300 nm as the principal emission wavelength choices.

(*Z*)-Phenylmethyldiazene 1-Oxide (5a). To a solution of 4.42 g (0.094 mol) of *N*-methylhydroxylamine in 200 ml of water and 100 ml of THF, buffered at pH 6.85 with 400 mg of *N*-methylhydroxylamine hydrochloride, at 0° was added (dropwise) a solution of 10.0 g (0.093 mol) of nitrosobenzene in 30 ml of THF. After the 3-h addition, the solution was stirred for an additional 3 h at 0°, at which time the pH was 4.8. The reaction mixture was diluted with 100 ml of water and extracted with 3 × 150 ml of pentane. The pentane extracts were washed with 2 × 150 ml of 1 N HCl, washed with 2 × 150 ml of water, and then dried (Na_2SO_4). Fractionation, in vacuo, of the yellow-green organic concentrate gave 8.55 g (68%) of **5a**, bp 49° (0.1 mm), and the pot residue contained 1.74 g (19%) of diphenyldiazene oxide (azoxybenzene), mp 34–36°. The spectral data for **5a** have been reported previously.[27]

(*Z*)-*tert*-Butylmethyldiazene 1-Oxide (5b). Methylhydroxylamine hydrochloride (4.34 g, 52 mmol) was added, under nitrogen, to a solution of KOH (3.09 g, 55 mmol) in 100 ml of absolute ethanol. After stirring briefly the ethanolic suspension was treated with 4.35 g (25 mmol) of 2-methyl-2-nitrosopropane dimer. The mixture was stirred for 2 h at room temperature and for 16 h at 38°, after which dilution with 100 ml of 1 N HCl, extraction with pentane (10 × 10 ml), drying (Na_2SO_4), and distillation (1 atm) gave a colorless concentrate. Distillation of the concentrate gave 3.03 g (52%) of 99% pure **5b**: bp 84–88° (104 mm); uv λ_{max} 215 nm (ε 6300) with inflection at 270 nm (ε ~1000); NMR see Table III. The spectral data for **5b** agreed with previously published data.[10,26] A second preparation gave 96% pure **5b** in 73% yield.

In a second approach, 0.14 g (11 mmol) of *N*-*tert*-butylhydroxylamine hydrochloride, neutralized and buffered at pH 6.1 in 15 ml of methanol, was condensed with 0.045 g (5.5 mmol) of nitrosomethane dimer, under irradiation (lamp R, 300 nm) for 4 h. Dilution with water, extraction with ether, and distillation (1 atm) of the solvent gave a concentrate to which was added a weighed amount of CH_2Cl_2. Integration of the NMR spectrum showed that 79 mg (6.8%) of **5b** had been formed, but no detectable amount of **6b** was present. VPC analysis confirmed the low yield of **5b** (column C).

(*Z*)-Methyl-*tert*-butyldiazene 1-Oxide (6b). Small samples of what is likely **6b** could be obtained, contaminated by **5b**, by preparative VPC of the following "photothermal" rearrangement experiments on **5b**. Solutions of **5b** (1% weight to volume) in pentane were irradiated as follows: (1) for 5 h in quartz by lamp R (254 nm) to give six compounds (VPC, columns A or C) including **5b** (73%) and **6b** (4%); (2) for 3 h in quartz by lamp R (300 nm) to give five compounds (VPC) including **5b** (90%) and **6b** (4%). (The percentages are relative VPC peak areas). NMR spectra of the mixtures of **5b** and **6b** obtained by preparative VPC gave the signals for **6b** recorded in Table III. The data for **6b** seem to agree with that obtained by previous authors,[10,26] who suggest the same structure.

(*Z*)-Ethylmethyldiazene 1-Oxide (5c). A solution of 0.55 g (0.024 mol) of sodium in 10 ml of methanol was added to a methanol solution of 2.0 g (0.024 mol) of *N*-methylhydroxylamine hydrochloride. The resulting white precipitate was removed by filtration and the filtrate was added, dropwise, to 1.18 g (0.01 mol) of nitrosoethane dimer[1b] which had been dissolved in 3 ml of methanol. The mixture was stirred for 3 days under a nitrogen atmosphere, diluted with 30 ml of dilute HCl, and extracted with 4 × 20 ml of ether. The residue from concentration at atmospheric pressure was subjected to preparative VPC (column C) to yield **5c** (retention time 0.7 relative to **6c**): ir (neat) 1518 and 1323 cm^{-1}; NMR, see Table III.

Anal. Calcd for $C_3H_8N_2O$: C, 40.89; H, 9.15; N, 31.80. Found: C, 40.95; H, 9.39; N, 31.70.

(*Z*)-Methylethyldiazene 1-Oxide (6c). This azoxyalkane was isolated by preparative VPC from the preceding experiment, **5c**/**6c** ratio ~2: ir (neat) 1504 and 1325 cm^{-1}; NMR, see Table III.

Anal. Calcd for $C_3H_8N_2O$: C, 40.89; H, 9.15; N, 31.80. Found: C, 40.60; H, 9.34; N, 31.98.

(*Z*)-Cyclohexylmethyldiazene 1-Oxide (5d). A solution of 4.6 g (0.055 mol) of *N*-methylhydroxylamine hydrochloride in 95 ml of methanol was neutralized (pH 10.2) by the dropwise addition of a saturated potassium hydroxide–methanol solution. The resulting solution was buffered at pH 6.97 by the further addition of 1.8 g of *N*-methylhydroxylamine hydrochloride and was cooled to 0° in a Pyrex photochemical immersion well. To this cooled solution, by dropwise addition over 0.75 h, was added 5.65 g (0.025 mol) of nitrosocyclohexane dimer[32] in 160 ml of methanol. At the same time, the reaction was irradiated with a uv lamp (lamp R, 350 nm) with aliquots being periodically removed for VPC analysis (column A). After 10.5 h (complete reaction) the mixture was diluted with 150 ml of water and extracted thoroughly with pentane (total volume 375 ml). The pentane extracts were dried (Na_2SO_4), concentrated (1 atm), and distilled in vacuo to give 5.88 g (83%) of a mixture of **5d** and **6d**, bp 65° (3.0 mm), **5d/6d** ratio 11. Preparative VPC (column C) gave pure **5d**: uv λ_{max} 214 nm (ϵ 6000) with an inflection at 280 nm (ϵ ~20) observable at higher concentrations; NMR, see Table III.

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.27; H, 9.91; N, 19.92.

(*Z*)-Methylcyclohexyldiazene 1-Oxide (6d). This azoxyalkane was isolated from the preceding experiment by preparative VPC: uv λ_{max} 222 nm (ϵ 7600); NMR, see Table III.

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.18; H, 9.63; N, 19.95.

Thermally Induced Condensations Yielding 5d and 6d. A. A solution of 0.231 g (0.0275 mol) of *N*-methylhydroxylamine hydrochloride was neutralized (pH 10.4) with saturated potassium hydroxide in methanol and was then buffered at pH 6.9 by the further addition of 0.10 g of the hydrochloride salt. After the addition of 0.280 g (0.0125 mol) of nitrosocyclohexane dimer in 25 ml of methanol the mixture was heated at reflux for 8 h. After dilution with water, extraction, and drying, the organic extract was analyzed by VPC (column A) using naphthalene as internal standard. The analysis indicated the formation of 0.24 g (70.3%) of **5d**, 0.050 g (14.1%) of **6d**, and 7% of cyclohexanone oxime.

B. A solution of 9.2 g (0.11 mol) of *N*-methylhydroxylamine hydrochloride in 30 ml of methanol was neutralized (pH 10.8) as before and then buffered at pH 6.98 by the further addition of 5 g of the hydrochloride salt. To this was added a solution of 11.3 g (0.050 mol) of nitrosocyclohexane dimer in 75 ml of THF and the resulting mixture was heated at reflux for 18 h. After dilution with 250 ml of water, the mixture was subjected to continuous extraction with 100 ml of pentane. After drying (Na_2SO_4) the pentane extract was concentrated and the concentrate was subjected to column chromatography on 200 g of silica gel. Fractions eluted with mixtures of pentane and methylene chloride were monitored by VPC analysis (column A); 20–40% CH_2Cl_2 in pentane gave pure **5d**, 9.0 g (63%) after short-path distillation, bp 61° (3.8 mm); 50–75% CH_2Cl_2 in pentane gave a mixture of **5d** and **6d**, 2.28 g (16%) after distillation in vacuo; and elution with 100% CH_2Cl_2 gave 98% pure **6d**, 2.26 g (16%) after distillation, bp 66° (3.8 mm). In the crude reaction mixture, VPC analysis indicated a **5d/6d** ratio of 2.7.

Preparation of 5d and 6d Using *N*-Cyclohexylhydroxylamine. A solution of 0.34 g (0.0030 mol) of *N*-cyclohexylhydroxylamine[33] in 10 ml of methanol was buffered at pH 6.89 by addition of a solution of the corresponding hydrochloride salt. To this was added 0.115 g (0.013 mol) of nitrosomethane dimer[1b] and the resulting mixture was irradiated (lamp R, 300 nm) for 8.5 h with cooling by an air circulating fan only. VPC analysis (column A) using an internal standard indicated the formation of 0.142 g (38.5%) of **5d**, 0.0217 g (5.9%) of **6d**, 10% of cyclohexanone oxime, plus unreacted *N*-cyclohexylhydroxylamine.

Directed Synthesis of 5d. A solution of 0.985 (0.010 mol) of *N,O*-dimethylhydroxylamine hydrochloride in 1 ml of H_2O was neutralized (pH 11.4) with saturated aqueous potassium hydroxide and was then buffered at pH 5.75 by the further addition of 60 mg of the hydrochloride salt. To this was added 0.057 g (0.025 mol) of nitrosocyclohexane dimer in 8 ml of THF after which the mixture was heated at 50° for 12 h. The usual work-up gave a concentrate which was analyzed by NMR spectroscopy using a weighed amount of CH_2Cl_2 as an internal standard. The only azoxyalkane was **5d**, 0.040 g (55.8%), and this was confirmed by VPC analysis (column A) which also showed the presence of cyclohexanol and cyclohexanone.

Directed Synthesis of 6d. A solution of 0.066 g (0.004 mol) of *N*-cyclohexyl-*O*-methylhydroxylamine hydrochloride in 2 ml of H_2O was neutralized with saturated aqueous potassium hydroxide. The resulting organic solid was extracted with 4 × 1.5 ml of THF and this extract was buffered at ~pH 4.6 by the further addition of the hydrochloride salt. To this was added 0.018 g (0.2 mmol) of nitrosomethane dimer[1b] and the resulting mixture was irradiated (lamp R, 300 nm) in a Pyrex vessel for 8 h. VPC analysis (column B) using tetradecane as an internal standard indicated the formation of 0.0090 g (16%) of **6d** as the only azoxyalkane. A substantial amount of unreacted starting hydroxylamine was detected.

***N*-Cyclohexyl-*O*-methylhydroxylamine Hydrochloride.** A solution of 0.46 g (0.029 mol) of ethyl *N*-methoxy-*N*-cyclohexylcarbamate and 0.40 g (0.072 mol) of potassium hydroxide in 3 ml of methanol and 0.5 ml of H_2O was refluxed for 24 h. After extraction with ether (5 × 5 ml) and drying (Na_2SO_4), the extract was concentrated to 5 ml volume and excess saturated 2-propanol–HCl was added. This solution was evaporated to dryness with the last traces of water being removed by azeotropic distillation with benzene. The resulting hydrochloride salt was recrystallized from methanol–ether to give 0.23 g (63%) of white crystals: mp 143–144.5°; NMR (D_2O) δ 3.45 (m, 1 H, cyclohexyl methine H), 3.9 (s, OCH_3).

Anal. Calcd for $C_7H_{15}ClNO$: C, 50.76; H, 9.57. Found: C, 50.88; H, 9.97.

Ethyl *N*-Methoxy-*N*-cyclohexylcarbamate. To a rapidly stirred solution of 0.94 g (0.050 mol) of ethyl *N*-hydroxy-*N*-cyclohexylcarbamate and 0.52 g (0.093 mol) of potassium hydroxide in 8 ml of methanol at 0° was added 0.6 ml (0.095 mol) of methyl iodide. The mixture was stirred for 1 h at 0° and then at reflux temperature for 8 h. The addition of 50 ml of pentane precipitated the potassium iodide, and, after drying and concentration the crude product, 0.56 g (46%), was chromatographed over 8 g of silica gel. Elution with 10% ether in pentane gave 0.5 g of a colorless liquid which was distilled at 62° (0.5 mm) to give the analytically pure product: NMR ($CDCl_3$) δ 4.21 (q, OCH_2), 3.70 (s, OCH_3), 1.31 (t, CH_3).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52. Found: C, 59.66; H, 9.58.

Ethyl *N*-Hydroxy-*N*-cyclohexylcarbamate. Ethyl chloroformate (1.73 ml, 0.018 mol) was added dropwise to a solution of 2.08 g (0.018 mol) of *N*-cyclohexylhydroxylamine[33] and 1.95 g (0.018 mol) of Na_2CO_3 in 15 ml of H_2O and 65 ml of THF at 0°. The mixture warmed to room temperature while being stirred for 3 h. The reaction was neutralized (litmus) by adding 6 N HCl and the product was isolated by extraction with ether (3 × 50 ml), drying (Na_2SO_4), and concentration in vacuo. Chromatography over 60 g of silica gel (eluent pentane, ether) gave 2.24 g (66%) of product which was further purified by molecular distillation at 65° (0.15 mm): ir ($CHCl_3$) 3300 and 1670 cm^{-1}; NMR ($CDCl_3$) δ 4.16 (q, OCH_2), 3.75 (m, cyclohexyl methine H), and 1.27 (t, CH_3).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.75; H, 9.15; N, 7.48. Found: C, 58.01; H, 9.22; N, 7.31.

(*Z*)-Benzylmethyldiazene 1-Oxide (5e). A solution of 0.095 g (0.0011 mol) of *N*-methylhydroxylamine hydrochloride in 1 ml of H_2O was neutralized and buffered (pH 6.2) as previously mentioned. To this was added 0.12 g (0.5 mmol) of α-nitrosotoluene dimer[32] in 10 ml of methanol and the resulting solution was irradiated (lamp R, 300 nm) through Pyrex for 4 h with cooling by air circulation only. An aliquot of the reaction was extracted with ether, and after drying (Na_2SO_4) and concentration, was analyzed by NMR spectroscopy. The **5e/6e** ratio thus obtained was 2.46 (integration of CH_3 and CH_2 signals) and the ratio was seen to increase with time. This aliquot was then analyzed by VPC, using nitrobenzene as internal standard (column C), the results of which indicated the formation of 0.059 g (39.3%) of **5e**; thus the yield of **6e** was 16% and the total yield 53%. Pure **5e** could be separated from benzaldehyde oxime by chromatography over 15 g of alumina (neutral or basic), eluting with pentane, followed by molecular distillation: ir ($CDCl_3$) 1506 and 1280 cm^{-1}; uv λ_{max} 273 nm (ϵ 350) and 278 (225); both are peaks on strong end absorption with ϵ ~10^4 at 210 nm; NMR, see Table III.

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.70; H, 6.94; N, 18.75.

(*Z*)-Methylbenzyldiazene 1-Oxide (6e). A small sample of this azoxyalkane could be obtained by silica gel chromatography of the preceding experiment, a technique which failed to separate **5e** from benzaldehyde oxime. Elution with ether gave **6e**, the most polar compound of the three: ir ($CDCl_3$) 1500 and 1260 cm^{-1}; NMR, see Table III.

(*Z*)-1-(1-Phenylethyl)methyldiazene 1-Oxide (5f). A solution of 0.095 g (1.2 mmol) of *N*-methylhydroxylamine hydrochloride in 1 ml of H_2O was neutralized and buffered (pH 6.2) as previously described. To this was added 0.135 g (0.5 mmol) of 1-nitroso-1-phenylethane dimer[34] in 10 ml of methanol, and the resulting solu-

tion was irradiated (lamp R, 350 nm) at 10° (water circulation) for 3 h. VPC analysis of the reaction using sulfolane as internal standard indicated the formation of 0.104 g (64%) of **5f**, 0.027 g (16%) of **6f**, and 0.017 g (13%) of acetophenone oxime. From an experiment using the same quantities of reactants, but which was heated at reflux for 14 h, VPC analysis showed the formation of 0.067 g (41%) of **5f**, 0.055 g (41%) of acetophenone oxime, and, by NMR analysis, 0.26 g (18%) of **6f**. From an experiment increased in scale by a factor of 10, and heated at reflux for 14 h, pure **5f** (0.5 g, 30%) could be isolated by chromatography over 20 g of silica gel (eluting with 10% ether in pentane) followed by molecular distillation at 68° (1 mm): ir ($CHCl_3$) 1510 cm^{-1}; uv λ_{max} 257, 263, and 268 nm (ϵ ~300) as peaks on strong end absorption (ϵ ~10^4 at 210 nm) plus an inflection at 280 nm (~150); NMR, see Table III.

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.85; H, 7.49; N, 16.82.

(*Z*)-Methyl-2-(1-phenylethyl)diazene 1-Oxide (6f). This azoxyalkane could be isolated from the preceding preparative experiment by preparative VPC (column D): uv λ_{max} no resolved maxima on a strong end absorption ϵ ~10^4 at 220 nm; NMR, see Table III.

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37, N, 17.06. Found: C, 65.76; H, 7.08; N, 16.86.

(*Z*)-*o*-Tolylmethyldiazene 1-Oxide (5g). A solution of 2.78 g (0.033 mol) of *N*-methylhydroxylamine hydrochloride in 50 ml of H_2O was neutralized and buffered (pH 6.7) as in previous experiments and then cooled to 0°. To this was added 3.03 g (0.030 mol) of o-nitrosotoluene in 200 ml of THF and the resulting solution was stirred for 14 h. The mixture was diluted with 300 ml of H_2O and extracted with 3 × 100 ml of benzene. The benzene extract was washed with 1 N HCl, with H_2O, dried (Na_2SO_4), and concentrated to give 3.4 g of liquid. NMR analysis using a weighed amount of CH_2Cl_2 as internal standard indicated the formation of 2.7 g (60%) of **5g**, 0.3 g (7%) of **6g**, and about 0.4 g (18%) of di-*o*-tolyldiazene oxide [by integration of the *N*-methyl signals of **5g** and **6g** and the *C*-methyl signals (~δ 2.5) of the diarylazoxy compound]. Analytically pure **5g** was isolated by fractional distillation of the reaction mixture: 1.34 g (30%), bp 67° (1.2 mm); ir ($CHCl_3$) 1490, 1375, and 1320 cm^{-1}; uv λ_{max} 223 nm (ϵ 7700) and 264 (1500); NMR, see Chart I and Table III.

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71. Found: C, 63.79; H, 6.72.

(*Z*)-Methyl-*o*-tolyldiazene 1-Oxide (6g). This azoxyalkane could be isolated from the preceding experiment by preparative VPC (column C) of higher boiling distillation fractions: ir ($CHCl_3$) 1500, 1420, and 1340 cm^{-1}; uv λ_{max} 228 nm (ϵ 9800) and 294 (5600); NMR, see Chart I and Table III; mol wt, calcd, 150.0793; found, 150.0784.

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Registry No.—**5a**, 35150-71-1; **5b**, 57497-28-6; **5c**, 57497-29-7; **5d**, 35214-91-6; **5e**, 57497-30-0; **5f**, 57497-31-1; **5g**, 57497-32-2; **6b**, 57497-33-3; **6c**, 57497-34-4; **6d**, 57497-35-5; **6e**, 57497-36-6; **6f**, 57497-37-7; **6g**, 57497-38-8; azoxybenzene, 495-48-7; *N*,*O*-dimethylhydroxylamine HCl, 6638-79-5; *N*-cyclohexyl-*O*-methylhydroxylamine HCl, 57497-41-3; ethyl *N*-methoxy-*N*-cyclohexylcarbamate, 57497-42-4; ethyl *N*-hydroxy-*N*-cyclohexylcarbamate, 57497-43-5; methyl iodide, 74-88-4; ethyl chloroformate, 541-41-3; *N*-cyclohexylhydroxylamine, 16649-50-6.

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Aliphatic Azoxy Compounds. V. Functionalization of (Z)-Phenylmethyldiazene 1-Oxide[1]

K. Grant Taylor* and Melvin S. Clark, Jr.

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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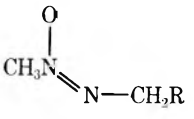
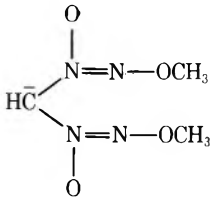
A study of the chemical transformations at the methyl group of azoxy compound (*Z*)-phenylmethyldiazene 1-oxide (**4a**) has been made. NBS bromination of **4a** gave (*Z*)-phenylbromomethyldiazene 1-oxide (**5a**), which was used as a substrate for the preparations of compounds **5b–k**. Silver ion assistance gave rapid substitution by oxygen nucleophiles, while strong bases effected a rapid fragmentation of **5a**. Nucleophiles that are weak bases successfully displaced the bromine atom of **5a**. Under neutral conditions, phenylhydroxymethyldiazene 1-oxide (**5b**) decomposed by way of phenyldiazonium ion, a route analogous to the neutral decomposition of methylazoxymethanol (**1b**). Under mildly basic conditions **5b** rapidly decomposed via a pathway initiated by proton abstraction from the CH_2 group of **5b**, yielding phenyldiimide as an intermediate. The sum of the transformations studied indicate that the azoxy group can stabilize a positive charge, an unpaired electron, or a negative charge at the C atom bound to the unoxidized N atom.

Chemical reactions that occur at the carbon atoms adjacent to an azoxy functional group have received little attention until fairly recently. Thus, Matsumoto and co-workers'[2] synthesis of MAM acetate (**1c**) from azoxymethane (**1a**) was not only valuable for its synthetic result, but also



1a, R = H
b, R = OH
c, R = $OCOCH_3$



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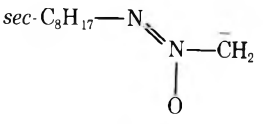
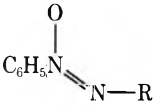


3

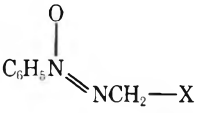
useful as a gauge of the relative reactivities at the proximal[3] and distal[3] α-carbon atoms of an azoxyalkane. The formal structural similarity between nitroalkanes and the proximal terminus of azoxyalkanes has been responsible for the long-held supposition that the two molecules should show similarity in C–H acidity. This similarity was borne out in experiment by Woodward and Wintner,[4] who examined the alkylation and H–D exchange of anion **2**, and by Moss and Love,[5] who examined the alkylation of anion **3**. However, given two equivalent[5b] α-alkyl groups, it is the *distal* rather than proximal α-H which displays the higher (kinetic) acidity. Thus, in azoxymethane (**1a**), the distal α-H's underwent base-catalyzed H–D exchange more rapidly.[6]

We were interested in examining the chemistry at the distal α-carbon atom of azoxyalkanes. It is this position on azoxyalkanes which suffers biological oxidation,[7] a transformation which turns the molecules into alkylating agents (the proximal alkyl group is transferred[6,8]) and hence (presumably) into potent carcinogens toward experimental animals.[7] Apart from Matsumoto's[2] work, little[9] has been reported concerning the chemistry at this carbon atom. We report herein on the functionalization of phenylmethyldiazene 1-oxide (**4a**)[1b] at the distal methyl group, and on some of the transformations of **5b**, a phenyl analogue of the carcinogenic MAM (**1b**).

Functionalization Reactions. Following Matsumoto's



4a, R = CH_3
b, R = CD_3

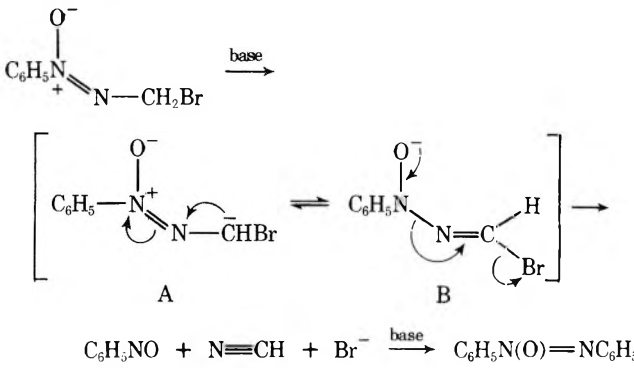


5a, X = Br
b, X = OH
c, X = $OCOCH_3$
d, X = OCH_3
e, X = OC_2H_5
f, X = O-*i*-C_3H_7
g, X = $OCH_2CH{=}CH_2$
h, X = $^+N(CH_3)_2CH_2CH_2OH$, Br^-
i, X = $-SC(NH_2)_2^+$, Br^-
j, X = SCN
k, X = Cl

lead,[2] we brominated **4a** using the Wohl–Ziegler reaction. Thus, refluxing **4a** in CCl_4 with *N*-bromosuccinimide and benzoyl peroxide gave crystalline, red-orange **5a**, in 70% yield, after silica gel chromatography. Bromination with molecular bromine also gave **5a**, but in poor yields. This free-radical transformation, together with those reported by Matsumoto[2] and Woodward and Wintner,[9] give indication that the azoxy function is capable of stabilizing an unpaired electron on the distal α-carbon atom (presumably via π-electron delocalization). Bromo compound **5a** was the substrate used for subsequent transformations.

Optimal substitution of **5a** by oxygen nucleophiles required silver ion assistance. Thus silver acetate–acetic acid treatment[2] of **5a** at room temperature rapidly converted it to crystalline **5c** in 80% yield. By contrast, the same transformation using sodium acetate required reflux temperature and longer reaction time. The conversion of **5a** to alcohol **5b** was smoothly effected using conditions similar to the Koenigs–Knorr reaction for converting glycosyl halides to free sugars or acetals: acetone–water, 25°, Ag_2CO_3. Alcohol **5b** was a stable, crystalline, off-white solid obtained consistently in 65–85% yields. Acetylation of **5b** gave **5c**. With the addition of calcium sulfate as a water scavenger, the Koenigs–Knorr conditions were applied to the syntheses of ethers **5d–g**. Other silver salts were tried in addition to silver carbonate. For example, silver nitrate assisted coupling of **5a** and allyl alcohol gave, in addition to **5g**, a product tentatively characterized as the nitrate ester of **5b** [**5**, X = ONO_2; ir 1650 and 1270 cm^{-1}; NMR δ 6.0 (s, ~2 H, NCH_2O)]. The methyl ether **5d** was also conveniently prepared using silver perchlorate in methanol, but with other

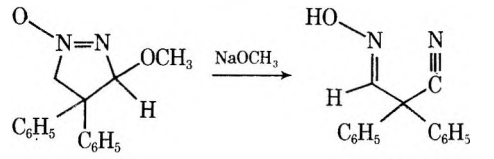
Scheme I



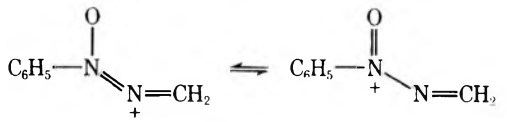
$$C_6H_5NO + N{\equiv}CH + Br^- \xrightarrow{\text{base}} C_6H_5N(O){=}NC_6H_5$$

alcohols, for example, allyl alcohol, this silver salt gave, again, a by-product in small amounts which was, in this instance, a shock-sensitive solid.

The attempted conversion of **5a** to ether **5d** using sodium methoxide in methanol led to the rapid fragmentation reaction shown in Scheme I. The products, nitrosobenzene, cyanide ion, and bromide ion, were all identified, as was azoxybenzene (produced from nitrosobenzene in a secondary reaction[10,11]). Other strong bases such as sodium hydroxide and the sodium salts of diethyl malonate and nitromethane also effected the fragmentation, as did weaker bases such as cyanide ion and amines (mixture of fragmentation and substitution). The initial reaction must be a proton abstraction by the base to give the anion A (Scheme I), which, presumably, can equilibrate with tautomeric form B. From tautomer B, Grob-type fragmentation yields the products shown. Some chemical support for the existence of tautomer B will be provided in a subsequent section. Jones and Northington[12] reported a similar fragmentation of cyclic azoxy compound **6**, using sodium methoxide in methanol, to give **7**. The initial step was the removal of the proton from the distal α-C atom.



6 **7**



8a **8b**

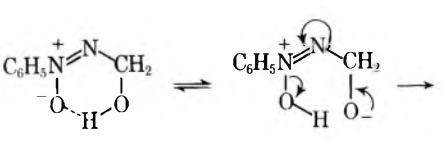
Nucleophiles which were weak bases did yield substitution products. As mentioned above, amines gave a mixture of fragmentation (major) and substitution (minor). However, the products of such substitution, e.g., **5** (X = NH-*i*-C_3H_7), being basic and carrying the seeds of their own destruction, were not stable. Interestingly, the tertiary amine *N,N*-dimethylethanolamine gave a substitution product, **5h**, in 64% yield. That **5a** had reacted with the ethanolamine with attack by nitrogen rather than attack by oxygen was indicated by the ir spectrum (KBr) of **5h**, which has a strong absorption at 3300 cm^{-1} for OH stretch, as does the ir spectrum of choline iodide. In addition, the ir spectra of both compounds had a band at 1470 cm^{-1} ($-CH_2-N^+{\equiv}$ bend) and lacked a 2700-cm^{-1} band for $-NH^+-$stretch. Thiourea reacted smoothly to give **5i** in 89% yield. The sulfur nucleophile thiocyanate ion also reacted readily with **5a**, but the product **5j**, an oil and a single spot in TLC, was unstable and could not be purified for elemental analysis by either distillation or preparative VPC. However, the ir spectrum (2160 cm^{-1}, $-SC{\equiv}N$ stretch) and the NMR spectrum (see Table I) are consistent with structure **5j**. Further, the C–S linkage in **5j** was further supported by the partial acid-catalyzed isomerization[13] of thiocyanate **5j** to a mixture of **5j** and the corresponding isothiocyanate, **5** (X = NCS, ir 2070 cm^{-1}). Lastly, lithium chloride in DMF or acetone gave **5k** in a classic SN2-type displacement reaction.

From the above, it is apparent that, toward substitution reactions, bromide **5a** reacts rapidly with nucleophiles, as would be expected for a primary halide. Thus reactions leading to products **5h–k** are complete in 0.5–1 h at room temperature. However, **5a** is extraordinarily reactive, for a primary halide, toward silver ion assisted substitutions. Thus, **5a** is consumed in minutes at room temperature upon dissolution in solvents containing dissolved silver ion. In an analysis of substitution processes at carbon atoms bound to the azo function, McBride and Malament[14] concluded that the azo group stabilizes adjacent carbonium ions by n-electron delocalization. At present, there is no experimental data which permits a decision between n stabilization (**8a**) or π stabilization (**8b**) or stabilization by both processes (**8a** ⇄ **8b**) of the azoxy cation, **8**, that must result upon reaction of **5a** with Ag^+. In any event, the data indicate that the azoxy group stabilizes an electron-deficient distal α-carbon atom.

Decomposition Reactions of 5b. The decomposition of MAM (**1b**) in the presence of RNA or DNA, in vitro or in vivo, results in the methylation of RNA or DNA as determined by an increase in the amount of 7-methylguanine.[7,15] Diazomethane has often been postulated as the reactive methylating intermediate.[16] Recent evidence obtained from the decomposition of **1b** in neutral[8] or mildly acidic[6] media has shown that diazomethane is not an intermediate in these particular decompositions. Thus, reaction of **1c** in D_2O solution produced (in addition to H_2O, CH_2O, and N_2) CH_3OD, not the CDH_2OD which would have been formed if CH_2N_2 had reacted with solvent.[8] As a result of these experiments[6,8] it appears that methyldiazonium ion is the likely methylating agent produced by **1b**, and by analogy, phenyldiazonium ion should be produced by **5b**. Accordingly, we tested the decomposition of **5b** under neutral and mildly basic conditions. The results follow.

A solution of **5b** in Me_2SO-d_6 and D_2O was maintained at 92° and monitored by NMR spectroscopy. The reaction was observed to have a half-life of 20 h and the products were those that would be predicted by analogy with **1b**, namely, water, formaldehyde, nitrogen, and phenol. Scheme II outlines a possible reaction pathway. Solvent may be involved in the O to O proton transfer of the intramolecularly bonded proton of **5b**, but the formation of diphenyl ether when the decomposition was conducted in molten phenol renders as unlikely a completely intramolecular mechanism for the formation of phenol in Scheme II. The difference in stability between **5b** and **1b** ($t_{1/2}$ = 18.6 h at 37°) must reflect the stabilizing influence of the benzene ring, probably lowering the ground-state energy of **5b** relative to **1b**.

Scheme II



5b

$$C_6H_5\overset{+}{N}{\equiv}N + H_2CO \xrightarrow{D_2O} C_6H_5OD + N_2 + HOD + OH^-$$

Table I. Spectral Features and Elemental Analyses of Azoxyalkanes 5[a]

		Chemical shift, δ (Me$_4$Si)[b,c]							Anal, %					
									Calcd			Found		
5	X	*o*-C$_6$H$_5$	*m, p*-C$_6$H$_5$	CH$_2$	α	β	γ	Uv λ_{max},[d] nm (log ε)	C	H	N	C	H	N
a	Br[e]	8.2	7.5	5.40				265 (4.04)	39.00	3.28		39.30	3.43	
b	OH	8.2	7.5	5.20				246 (4.05)	55.25	5.30	18.41	55.44	5.35	18.45
c	$OCOCH_{3\alpha}$	8.2	7.5	5.60	2.18 (1)			250 (4.12)	55.67	5.19	14.43	55.70	5.32	14.43
d	$OCH_{3\alpha}$	8.2	7.4	5.01	3.50 (1)			246 (4.27)	57.82	6.07	16.86	58.00	6.24	17.14
e	$OCH_{2\alpha}CH_{3\beta}$	8.2	7.4	5.20	3.78 (4)	1.75 (3)			59.99	6.71		59.63	6.94	
f	$OCH_\alpha(CH_3)_{2\beta}$	8.5	7.6	5.36	4.10 (7)	1.36 (2)		248 (4.04)	61.84	7.27	14.43	61.67	7.27	14.20
g	$OCH_{2\alpha}CH_\beta{=}CH_{2\gamma}$	8.1	7.4	5.15	4.25 (m)	5.90 (m)	5.31 (m)		62.49	6.29		62.61	6.55	
h[e,f]	$\overset{+}{N}(CH_3)_{2\alpha}CH_{2\beta}CH_{2\gamma}OH$	8.5	7.8	5.38	3.45 (1)	3.19 (m)	4.18 (m)		43.20	5.89	13.73	43.40	5.92	13.90
i[f,g]	$SC(NH_2)_2^+$	8.1	7.6	5.37				260 (4.28)	32.97	3.80	19.24	33.01	3.73	19.20
j	SCN	8.2	7.3	5.23										
k	Cl	8.5	7.7	5.42				258 (4.04)	49.28	4.14		49.39	4.41	

[a] Satisfactory analytical data (±0.35%) for C, H, N for all compounds were submitted for review. Ed. [b] NMR solvents were CCl_4 for compounds **5a–d**,f,j,k; $CDCl_3$ for **5e**,g; D_2O (external Me_4Si) for **5h**; Me_2SO-d_6 for **5i**; all phenyl signals were multiplets; all distal CH_2 signals were singlets. [c] For the designations α, β, and γ see the columns headed by X; multiplicities of symmetrical signals are given in parentheses after the chemical shifts; more complex multiplets are indicated by m. [d] Solvent 95% ethanol. [e] Br: Calcd: 13.00. Found: 12.96. [f] Counterion is Br^-. [g] Br: Calcd: 26.10. Found: 26.00.

Scheme III

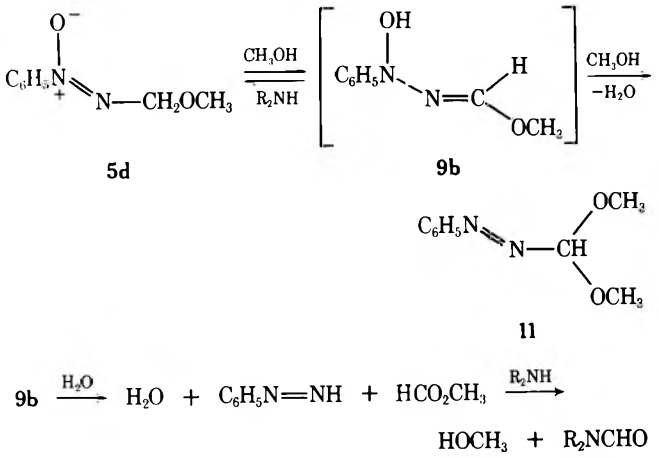
$$R_2N{-}CH{=}O + [C_6H_5N{=}N{-}D] \longrightarrow C_6H_5D + N_2$$

The decomposition of **5b** under basic conditions followed an entirely different course. Treatment of a methanol solution of **5b** with 1 equiv of methanolic sodium hydroxide at room temperature gave, immediately, a red solution followed by the rapid evolution of N_2. VPC analysis of the reaction after 1 h detected benzene (88% of theoretical) but *no* phenol or anisole. Use of the weaker base piperidine slowed the rate of decomposition permitting monitoring of the reaction by NMR spectroscopy. Upon addition of 1 equiv of piperidine to **5b** in CD_3OD the solution turned red and a slow evolution of N_2 started. NMR analysis after 2 min showed a weak CIDNP emission signal at δ 7.3 for benzene formed via phenyl *radical*. The major products (VPC analysis) of this reaction were benzene (29%), biphenyl (10%), and *N*-formylpiperidine (75%). Phenol and anisole were not present. The half-life of **5b** under these conditions was 2–3 h and the *N*-formylpiperidine formed in this reaction showed less than 5% deuterium incorporation in the formyl group. Scheme III can accommodate these results.

The removal (or C to O transfer) of the distal methylene proton from **5b** must be essentially irreversible since there was very little, if any, deuterium incorporated into the formyl group of *N*-formylpiperidine. We attribute this to a rapid dehydration step which converts tautomer **9a** to *N*-formyl-*N'*-phenyldiimide (**10**). Then, an amide interchange reaction transfers the formyl group yielding *N*-formylpiperidine and phenyldiimide. Phenyldiimide is known to undergo rapid decomposition in the presence of oxygen via the phenyl radical to give benzene and biphenyl.[17]

The reaction of methyl ether **5d** with piperidine in methanol gave results which support the reactions of Scheme III. From this reaction benzene (10%) and *N*-formylpiperidine (low yield) were detected, and a new compound, *N*-dimethoxymethyl-*N'*-phenyldiimide (**11**), was isolated (40%). When the decomposition was conducted in CD_3OD and monitored by NMR spectroscopy, a strong CIDNP emission singlet at δ 7.3 was observed for benzene. Hydrogen–deuterium exchange at the methylene group of **5d** was also observed, and NMR analysis of the *N*-formylpiperidine formed after 6-h reaction showed 32% deuterium incorporation in the formyl group. Scheme IV summarizes these results. The structure of azo compound **11**, also prepared from **5d** using triethylamine in methanol, was based on spectral data and elemental analysis. The UV spectrum showed maxima at 215 nm (ε 13 000) and 270 (1900), consistent with an aryl–alkylazo formulation, and the NMR spectrum showed signals for the following protons: *o*-phenyl at δ 7.7; *m*- and *p*-phenyl at δ 7.45; the formyl proton at δ 4.90; and the six methoxyl group protons at δ 3.5. Scheme IV suggests a possible route for the formation of *N*-formylpiperidine and phenyldiimide from **5d**, and while many mechanistic details are not clear (e.g., the mode of reaction of piperdine with **9b**), it does seem clear that the formation of compound **11** signals the trapping of an intermediate wherein the distal methylene group, formerly singly bound

Scheme IV



to N, has become doubly bound to N. We suggest structure **9b** for this intermediate. The methoxyl group of **9b** would prevent a dehydration step such as is proposed in Scheme III, **9a** → **10**, and, accordingly, we see that H–D exchange at the distal methylene group now can compete with the degradation reaction. Thus, the isolation of **11** serves as evidence for the intermediacy of **9b** in the reactions of Scheme IV, and, by implication, as evidence for **9a** and **10** of Scheme III as well as for B in Scheme I.

The observation of H–D exchange under mild conditions with **5d** indicated that proton abstraction from the distal carbon atom was reversible. Indeed, the piperidine-catalyzed exchange of the methyl hydrogens of **4a** was found to occur with ease at 25°C. Treatment of **4a** with 1 equiv of piperidine in CD_3OD–D_2O (5:1 by volume) gave **4b** with an exchange half-life near 0.5 h. The stability of **4** toward decomposition under these conditions was greater than for any other derivative studied. After 3 h, 89% of **4b** remained as evidenced by VPC analysis. Also, it is interesting to note that in the absence of D_2O, the exchange half-life increased by a factor of 4–5. Thus, the azoxy group appears capable of stabilizing negative charge at the distal carbon atom.

Summary. From the study of the foregoing reactions it appears that the azoxy group is capable of stabilizing a positive charge, an unpaired electron, or a negative charge at the distal carbon atom. Such diversity of character in a heteroatom-containing carbon functional group is rare, and is usually reserved for groups containing elements of the second row, e.g., sulfur. The base-induced decomposition studies with **5b** immediately suggest experiments which should be conducted on **1b**. The discovery of a free-radical decomposition pathway for MAM (**1b**) could have implications regarding the understanding of its mechanism of cancer induction. Finally, it is obvious that a number of questions remain unanswered, principally questions about the nature of the cationic and anionic intermediates and their possible synthetic utility. We hope to answer some of these questions with subsequent work.

Experimental Section

General. For instruments used see the Experimental Section of ref 1b. VPC analyses were performed on the following aluminum columns: column A, 4 ft × 0.125 in. 20% silicone oil Dow 710 on 60/80 mesh Chromosorb W (AW + DMCS); B, 4 ft × 0.25 in. 5% silicone oil Dow 710 on 60/80 Chromosorb W (AW + DMCS); C, 6 ft × 0.25 in. 5% silicone oil Dow 710 on 60/80 mesh Chromosorb W (AW + DMCS); D, 6 ft × 0.25 in. 5% silicone rubber UCW 98 on Diatoport S; E, 10 ft × 0.25 in. 20% SE-30 on 60/80 mesh Chromosorb W (AW + DMCS); F, 6 ft × 0.25 in. 5% silicone rubber UCW 98 on Chromosorb W (AW + DMCS); G, 6 ft × 0.125 in. silicone rubber UCW 98 on Diatoport S; H, 19 ft × 0.25 in. 25% SE-30 on Chromosorb W (AW + DMCS). NMR and uv spectral data and elemental analyses of compounds **5** are collected in Table I.

(*Z*)-Phenylbromomethyldiazene 1-Oxide (5a). A mixture of 5 g (36.8 mmol) of **4a**,[1b] 6.53 g (36.8 mmol) of *N*-bromosuccinimide, and 0.896 g (3.68 mmol) of benzoyl peroxide in 150 ml of carbon tetrachloride was refluxed for 24 h. After cooling and filtration, concentration of the filtrate in vacuo gave a red oil. Chromatography on 40 g of silica gel and elution with benzene gave 6.3 g of oil which crystallized upon addition of pentane and cooling: yield of **5a** 6.1 g (78%); mp 31–32°; ir (neat) 1490, 1410, 1340, and 1250 cm^{-1}.

(*Z*)-Phenylhydroxymethyldiazene 1-Oxide (5b). A mixture of 1.68 g (6 mmol) of silver carbonate, 10 ml of acetone, 5 ml of water, and 2.62 g (12 mmol) of **5a** was stirred at 25° for 24 h in the dark. Filtration followed by concentration in vacuo yielded a red oil. This was dissolved in chloroform, washed with three 50-ml portions of water, dried (Na_2SO_4), and reconcentrated in vacuo to give 1.5 g (88%) of yellow, crystalline **5b**, mp 57–59°. Recrystallization from pentane gave an analytical sample: mp 57–58°; ir (CCl_4) 3600 (sharp), 3470 (broad), 1490, 1380, 1340, and 1090 cm^{-1}; the ir spectra of appropriately diluted samples of **5b** in chloroform indicated that the 3470-cm^{-1} band was that of an intramolecularly H-bonded OH group.

(*Z*)-Phenylacetoxymethyldiazene 1-Oxide (5c). A solution of 470 mg (2.19 mmol) of **5a** and 365 mg (2.19 mmol) of silver acetate in 12 ml of glacial acetic acid was stirred at 25° for 1 h in the dark. After filtration (AgBr), concentration of the filtrate in vacuo gave a yellow oil which crystallized upon the addition of ether to give 355 mg (78%) of **5c**, mp 40–42°. Recrystallization from ether–pentane gave an analytical sample: mp 41–44°; ir (CCl_4) 1760, 1490, 1440, and 1215 cm^{-1}.

(*Z*)-Phenylmethoxymethyldiazene 1-Oxide (5d). To a solution of 1.07 g (4.97 mmol) of **5a** in 20 ml of anhydrous methanol was added 1.03 g (4.97 mmol) of anhydrous silver perchlorate dissolved in 10 ml of anhydrous methanol. Immediately, a yellow precipitate formed, but the mixture was stirred for 24 h at 25° in the dark. After filtration of the silver bromide the safest procedure is to mix the reaction solution with chloroform and wash thoroughly with water to remove all perchloric acid. *Failure to do this prior to concentration of the organic solvent has led to an explosion.* Concentration of the chloroform solution in vacuo yielded 680 mg of an orange oil. VPC analysis (column D) showed one major component and no **5a**. Preparative VPC (column D) gave an analytical sample of **5d**: ir (neat) 1490, 1440, and 1340 cm^{-1}.

(*Z*)-Phenylisopropoxymethyldiazene 1-Oxide (5f). To a mixture of 0.077 ml (4 mmol) of 2-propanol, 0.276 g (2 mmol) of silver carbonate, and 0.150 g of dried calcium sulfate in 5 ml of benzene was added 0.215 g (1 mmol) of **5a** dissolved in 3 ml of benzene. After stirring at 25° for 24 h in the dark under a nitrogen atmosphere, the mixture was filtered and the filtrate concentrated in vacuo to give 0.150 g of a red oil. NMR analysis showed that the oil contained ~3% of alcohol **5b** in addition to **5f**. Preparative VPC (column E) using low instrument temperatures gave an analytical sample of **5f**.

(*Z*)-Phenylethoxymethyldiazene 1-Oxide (5e). The procedure outlined above for **5f** was used for the preparation of **5e**, to give 150 mg of crude **5e** from 215 mg of **5a**. Preparative VPC (column F) gave an analytical sample of **5e**: ir ($CHCl_3$) 1490, 1440, and 1340 cm^{-1}.

(*Z*)-Phenyl-(2-propenoxy)methyldiazene 1-Oxide (5g). The procedure outlined above for **5f** was used for the preparation of **5g** to give 0.350 g of crude **5g** from 0.5 g of **5a**. VPC analysis (column C) showed one major component and no **5a**. Preparative VPC (column C) gave pure **5g**: ir (neat) 1650, 1495, 1275 cm^{-1}.

***N*-[(*Z*)-1-Phenyloxidodiazenylmethyl]-*N*,*N*-dimethylethanolammonium Bromide (5h).** To a solution of 0.215 g (1.0 mmol) of **5a** in 2 ml of acetone was added 0.089 g (1.1 mmol) of *N*,*N*-dimethylethanolmine. The solution turned red, and then, slowly, back to yellow with the formation of a white precipitate. The reaction mixture was stirred for an additional 30 min and then filtered to give 0.270 g of white crystals, mp 172–174°. Recrystallization from ethanol–ether gave 0.193 g (64%) of **5h**: mp 178–179°; ir (KBr) 3300 and 1470 cm^{-1}.

***S*-[(*Z*)-1-Phenyloxidodiazenylmethyl]isothiouronium Bromide (5i).** A solution of 25 mg (0.116 mmol) of **5a** and 8.86 mg (0.116 mmol) of thiourea in 1 ml of ethanol was stirred at room temperature for 1 h. The reaction mixture was poured into 30 ml of anhydrous ether and 30 mg (89%) of **5i** was collected as white crystals by filtration, mp 154–155°. Recrystallization from ethanol–ether gave an analytical sample, mp 154–155°.

(*Z*)-Phenylthiocyanatomethyldiazene 1-Oxide (5j). A solution of 0.905 g (9.3 mmol) of potassium thiocyanate in 25 ml of ace-

tone was added at 0° to a solution of 2.0 g (9.3 mmol) of **5a** in 23 ml of acetone. The mixture was warmed to room temperature, stirred for 24 h, and filtered (KBr). The filtrate was dried (Na_2SO_4) and concentrated in vacuo to give 1.75 g of red oil. Chromatography on 60 g of silica gel gave 1.1 g of red oil which showed one spot on thin layer chromatography (two systems). Attempts at molecular distillation and preparative VPC gave decomposition of **5j**: ir (neat) 2160, 1440, 1390 cm^{-1}.

A solution of 90 mg of **5j**, 0.5 ml of boron trifluoride etherate, and 10 ml of benzene was heated at 60° for 14 hr. After dilution with pentane, two washes with saturated $NaHCO_3$ solution, drying (Na_2SO_4), and concentration in vacuo, a small amount of red oil was obtained: ir (neat) 2170 (sharp), 2070 (broad), 1490, and 1320 cm^{-1} (azoxy group).

(Z)-Phenylchloromethyldiazene 1-Oxide (5k). A solution of 2.95 g (13.7 mmol) of **5a** and 4.24 g (100 mmol) of lithium chloride in 860 mg of acetone was heated at reflux for 3 h. The reaction mixture was further diluted with benzene and washed with water. After drying and evaporation of the organic layer (in vacuo) the crude product (2.49 g, 99% **5k**, 1% **5a** by VPC on column F) was distilled to give an analytical sample: bp 70° (0.25 mm); ir (neat) 1475, 1320, and 1270 cm^{-1}.

Decomposition of 5a under Basic Conditions. To a solution of 15 mg (0.070 mmol) of **5a** in 0.5 ml of methanol containing 3 μl of tetradecane (2.29 mg for VPC internal standard) was added 1 equiv of sodium hydroxide dissolved in 95% methanol. The reaction mixture immediately turned red; no gas was evolved. VPC analysis after 5 min showed 5% unreacted **5a**, plus nitrosobenzene and azoxybenzene (~85% combined). Cyanide ion was detected in an identical reaction using the ferric ferrocyanide "Prussian blue" test. A blank containing nitrosobenzene did not give the Prussian blue precipitate. In reactions of **5a** with other bases (see text) nitrosobenzene and azoxybenzene were detected by VPC analysis of reaction mixtures.

Decomposition of 5b under Neutral Conditions. A solution of 50 mg (0.34 mmol) of alcohol **5b**, 300 μl of Me_2SO-d_6, and 200 μl of D_2O in an NMR tube was maintained at 92° and monitored periodically by NMR analysis. The disappearance of **5b** had a half-life of about 20 h during which time the evolution of gas (N_2) was observed. At the half-life, the ratio of phenol-*O*-*d* to formaldehyde was 50:38. The presence of phenol was confirmed by VPC analysis (column B).

Decomposition of 5b under Basic Conditions. A solution of 31.8 mg (0.209 mmol) of **5b** and 20.6 μl (0.209 mmol) of piperidine in 350 μl of methanol-d_4 in an NMR tube was maintained at room temperature and monitored at regular intervals by NMR analysis. The evolution of gas (N_2) was observed throughout the reaction which had a half-life of about 2 h. An NMR spectrum taken at t = 19 h indicated 18% of unreacted **5b** and about 70% *N*-formylpiperidine (based on no D incorporation into **5b**). VPC analysis (internal standard, column A) at t = 19 h showed *N*-formylpiperidine (75%), benzene (29%), and biphenyl (10%) as the major products. The initial NMR spectrum of the reaction showed a weak CIDNP emission signal at δ 7.3 for benzene. In an experiment in which **5b** was decomposed with 1 equiv of methanolic sodium hydroxide, VPC analysis (internal standard column A) showed benzene (88%) as the major volatile product. In all of the basic decomposition reactions of **5b**, the reaction mixtures were examined by VPC analysis for products expected from the reactions of phenyldiazonium ion with the nucleophiles H_2O, CH_3OH, and piperidine. None were observed.

Phenyldimethoxymethyldiazene (11). A solution of 196 mg (1.18 mmol) of **5d** and 165 μl (1.18 mmol) of triethylamine in 6 ml of methanol was stirred for 48 h at 25°, and then concentrated in vacuo to a volume of 2 ml. VPC analysis of an aliquot (internal standard, column A) showed the presence of azo compound **11** (50%), starting material **5d** (20%), and benzene. Preparative VPC (column C) gave an analytical sample of **11**: ir (CCl_4) 2830, 1520, 1450, and 1320 cm^{-1}; uv (95% ethanol) λ_{max} 270 nm (ε 1900) and 215 (13 000); NMR (CCl_4) δ 7.70 (m, 2 H, *o*-phenyl H), 7.45 (m, 3 H, *m*-, *p*-phenyl H), 4.91 [s, 1 H, $-CH(OR)_2$], 3.51 (s, 6 H, OCH_3).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71. Found: C, 60.18; H, 6.99.

Decomposition of 5d under Basic Conditions. A solution of 23.7 mg (0.143 mmol) of **5d** and 14.1 μl (0.143 mmol) of piperidine in 2 ml of methanol was stirred at 25° for 30 h. VPC analysis (internal standard, column A) showed four major components: starting material **5d** (30%), **11** (40%), benzene (10%), and *N*-formylpiperidine (~20%).

A similar reaction using methanol-d_4 as solvent allowed the reaction to be monitored by NMR spectroscopy. At room temperature the disappearance of **5d** had a half-life approximating 3.5 h (with triethylamine, $t_{1/2} \simeq 6$ h) as estimated by monitoring the signals for the CH_2 and OCH_3 groups of **5d**. In the initial three NMR spectra of the reaction a strong CIDNP emission singlet at δ 7.3 for benzene was observed. At t = 6 h, integration of the signals at δ 7.85 (s, $HCONR_2$) and 2.9 (m, CH_2 groups bound to N of *N*-formylpiperidine) indicated about 32% deuterium incorporated into the formyl group of *N*-formylpiperidine. This observation was consistent with the observations of (1) a more rapid decay of the CH_2 signal of **5d** relative to the OCH_3 signal of **5d** and (2) the stability of *N*-formylpiperidine toward H–D exchange. The NCH_2 groups of piperidine, δ 2.7, were sufficiently separated from the analogous protons of the *N*-formyl derivative to permit an estimation of the extent of deuterium in the latter compound.

Phenyltrideuteriomethyldiazene 1-Oxide (4b). A solution of 36 mg (0.26 mmol) of **4a**, 26.1 μl (0.265 mmol) of piperidine, and 20 μl of methylene chloride (internal standard) in 300 μl of methanol-d_4–deuterium oxide (5:1 by volume) was placed in an NMR tube and maintained at 25°. The $t_{1/2}$ for deuterium exchange was determined by following the disappearance of the methyl group singlet of **4a**, and was found to be 30 min. VPC analysis (internal standard, column A) after 3 h reaction showed 89% of **4** present. The identity of **4** was checked by VPC analysis on column D.

Acknowledgment. The authors would like to thank Brandon Simons for the preparation and characterization of compound **5k**.

Registry No.—**4a**, 35150-71-1; **4b**, 57496-78-3; **5a**, 57496-79-4; **5b**, 57496-80-7; **5c**, 57496-81-8; **5d**, 57496-82-9; **5e**, 57496-83-0; **5f**, 57496-84-1; **5g**, 57496-85-2; **5h**, 57496-86-3; **5i**, 57496-87-4; **5j**, 57496-88-5; **5k**, 57496-89-6; **11**, 57496-90-9; *N*-bromosuccinimide, 128-08-5; silver carbonate, 534-16-7; silver acetate, 563-63-3; methanol, 67-56-1; 2-propanol, 67-63-0; *N,N*-dimethylethanolamine, 108-01-0; thiourea, 62-56-6; potassium thiocyanate, 333-20-0; lithium chloride, 7447-41-8.

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Aliphatic Azoxy Compounds. VI. Photolytic Isomerization of Azoxyalkanes and the Thermal Ring Opening of 2-Cyclohexyl-3-methyloxadiaziridine[1]

K. Grant Taylor,* S. Ramdas Isaac, and James L. Swigert

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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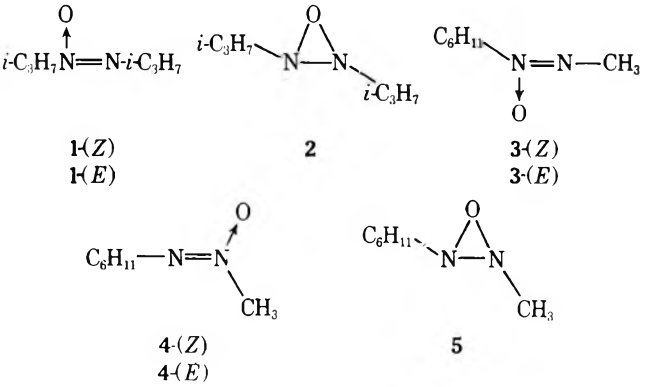
The photolysis of (*Z*)-bis(1-methylethyl)diazene *N*-oxide [1-(*Z*)] gave ring closure to oxadiaziridine **2** as the principal product accompanied by minor amounts of deoxygenation. Azoxyalkane 1-(*E*) was not obtained by direct photolysis of 1-(*Z*) owing to an unfavorable photoequilibrium strongly favoring 1-(*Z*); 1-(*E*) was obtained by thermolysis of **2** and, alternately, by peroxy acid oxidation of (*Z*)-azoisopropane. (*Z*)-Cyclohexylmethyldiazene 1-oxide [3-(*Z*)] and (*Z*)-methylcyclohexyldiazene 1-oxide [4-(*Z*)] gave both *Z* to *E* isomerization to their respective *E* isomers as well as ring closure to (*E*)-2-cyclohexyl-3-methyloxadiaziridine (**5**). The thermal ring opening of **5** was observed to give all four azoxyalkane isomers, 3-(*Z*) > 4-(*Z*) > 3-(*E*) > 4-(*E*), the ratios of which are determined principally by steric factors attending the ring opening. Acid catalysis of the ring opening of **5** (excess boron trifluoride etherate) enhances the yield of isomers **4**. Spectra and some properties of the *E* azoxyalkanes are discussed.

The photochemical reactions of the azoxy functional group have been studied in some detail[2] since Wacker's original observations in 1901[3] that 1,1′-azoxynaphthalene formed a red "oxy-azo" compound upon exposure to sunlight. Disregarding fragmentation[2] three types of reactions are found to occur: (1) deoxygenation to an azo compound via a triplet state;[4] (2) *Z*–*E* interconversion,[5] probably via a singlet state; (3) oxygen migration as manifested by (a) the formation of ortho (and para)[2,5c] hydroxyazoaryl compounds—the "photo-Wallach" rearrangement—and (b) oxadiaziridine formation[5d,6] or N to N′ oxygen migration[5e] which must proceed by way of the thermal ring opening of an oxadiaziridine intermediate. We have been interested in the oxadiaziridine-formation reaction for the purpose of preparing and firmly characterizing azoxyalkanes with *E* stereochemistry.[5e,f,7] In this paper we report on the photolytic isomerization of three azoxyalkanes, on some spectral aspects of three *E* azoxyalkanes, and on the thermal and acid-catalyzed ring openings of two oxadiaziridines.[10]

Photolyses. Small-scale test photolyses of azoxyalkane 1-(*Z*) indicated that irradiation at wavelengths above 300 nm (Pyrex low-wavelength cutoff) gave no reaction. In contrast, irradiation with a medium-pressure mercury lamp using a quartz reaction vessel resulted in the conversion of 1-(*Z*) to a new substance, with much shorter VPC retention time, which subsequently was shown to be oxadiaziridine **2**. In contrast with previous work with aryl–alkyl azoxy compounds,[5e] azoxyalkane 1-(*Z*) gave no 1-(*E*) upon irradiation. A preparative scale photolysis of 1-(*Z*) in pentane at ~10° for 17 h (with a Vycor filter to reduce decomposition, low-wavelength cutoff 210 nm) gave, by VPC analysis, 52% of **2**, 20% of recovered 1-(*Z*), and 28% of other compounds including (*Z*)- and (*E*)-azoisopropane, as well as some 1-(*E*) (produced by the ring opening of **2**). Oxadiaziridine **2** could be purified adequately by low-temperature distillation or column chromatography, but preparative VPC gave the purest samples.

The structure of **2** was indicated by the relatively high-field location of the α-CH NMR signal (entry 4, Table II) and by the thermal isomerization of **2** to 1-(*Z*) and 1-(*E*). Interestingly, the NMR signal of the β-methyl groups of **2**, which appeared as a sharp doublet in CCl_4, was split into a pair of doublets in the solvents acetone-d_6 and benzene (entries 5 and 6, Table II). 1,2-Diisopropyldiaziridine[11] also shows magnetically nonequivalent methyl groups, a fairly common observation for an isopropyl group bound to an asymmetric center,[12] but the solvent dependency of such nonequivalence was not observed for diaziridines.[11] The fact that **2** displays nonequivalent methyl groups means



that the isopropyl groups are bound to noninverting N atoms, a process which, in the cases of the companion *E* oxaziridine[13,14] and *E* diaziridine[14] ring systems, has an activation energy greater than 25 kcal mol^{-1}.

Azoxyalkane 1-(*E*) (with the isopropyl groups in a cis geometry) was initially prepared by peroxy acid oxidation of (*Z*)-azoisopropane. In contrast with 1-(*Z*), irradiation of 1-(*E*) at 350 nm did produce a reaction, namely conversion to 1-(*Z*). After 9 h a 1-(*Z*)/1-(*E*) ratio of 32 was obtained as determined by VPC analysis with no other products being observed. When an irradiation of 1-(*E*) in a quartz reaction vessel was monitored by VPC analysis, it was seen that *E* to *Z* conversion proceeded more rapidly than (and probably preceded) ring closure to **2**. VPC analysis of this reaction after 8 h showed ~2% of 1-(*E*), 82% of 1-(*Z*), and 16% of oxadiaziridine **2**. Thus, the high *Z*/*E* ratios observed in these photolyses of azoxyalkane 1-(*E*) indicate why no 1-(*E*) was observed in the photolyses of 1-(*Z*): the photoequilibrium concentration of 1-(*Z*) must be near 100%.

This high *Z*/*E* photoequilibrium ratio for azoxyalkanes **1** must reflect an unfavorable steric effect for formation of the *E* isomer of **1**, since direct *Z* to *E* conversion was effected by the photolyses of both 3-(*Z*) and 4-(*Z*). The photolyses of 3-(*Z*) and 4-(*Z*) were studied on both small and preparative scales using a medium-pressure Hg lamp and these latter results are summarized in Table I.[15] Thus, we see that isolable yields of 3-(*E*) and 4-(*E*) are produced from the corresponding *Z* isomers. To be sure, the relatively high yields are in part due to the low solubility of the *E* azoxyalkanes in alkane solvents, a factor which makes their preparation particularly convenient. However, when 3-(*Z*) was photolyzed in CD_3OD in which the *E* isomer is soluble, NMR analysis after 9.5 hr indicated that about 12% of 3-(*E*) was present, along with a low percentage of **5**.[16] This experiment also indicated that *Z*–*E* interconversion is fast-

Table I. Product Distribution after 2.5-h Photolysis of 3-(*Z*) and 4-(*Z*) in Pentane at −30°

Starting azoxyalkane	Products, % yield				
	3-(*Z*)	3-(*E*)	4-(*Z*)	4-(*E*)	5
3-(*Z*)	33[a]	28.5[b]	5	2.5	27[c]
4-(*Z*)	6	Trace	7[a]	19[b]	58[c]

[a] Isolated yield of recovered starting material accompanied by a lower percentage of the alternate *Z* isomer (as determined by NMR analysis). [b] Isolated by filtration of the reaction mixture and accompanied by a low percentage of the alternate *E* isomer (as determined by NMR analysis). [c] Isolated yield with purity >90%.

er than ring closure for compounds **3** in methanol, and the 12% yield is probably close to the *Z*–*E* photoequilibrium concentration of 3-(*E*). In comparison, the *Z*/*E* ratio at (or near) the rapidly established *Z*–*E* photoequilibrium for the phenyl counterpart of **3**, namely *N*-phenyl-*N*′-methyldiimide *N*-oxide, is 0.72.[5e] As the data of Table I indicates, azoxyalkane 4-(*Z*) was more readily converted to oxadiaziridine **5** than was 3-(*Z*). This photoreaction was most often used for preparations of **5**, which could be isolated by low-temperature chromatography or fractional distillation. The characterization of **5** rests on the relatively high field position of the prominent NMR signal of the *N*-methyl group, δ_{Me_4Si} ($CDCl_3$) 2.60 (singlet), and also on the thermal conversion of **5** to the four azoxyalkane isomers **3** and **4**.

We have formulated the oxadiaziridines **2** and **5** as *E* diastereomers. In this present work and in the work of Greene and Hecht[6] only a single oxadiaziridine was isolated from a given reaction. All known oxadiaziridines, including Greene's first[6a] di-*tert*-butyl example, have displayed approximately the same thermal stability toward ring opening. The only reasonable geometry for 2,3-di-*tert*-butyloxadiaziridine is *E*, and it is on the basis of this argument that we assign the *E* stereochemistry to **2** and **5**.

Structures and NMR Properties of *E* Azoxyalkanes. All three *E* azoxyalkanes, 1-(*E*), 3-(*E*), and 4-(*E*), had elemental analyses in agreement with the proposed structures, and all three were isomerized to the corresponding *Z* isomers. Thus, as mentioned above, photolysis of 1-(*E*) at 350 nm cleanly converted it to 1-(*Z*) which was identified by VPC analysis. Further, 4-(*E*) (mp 141°) was smoothly isomerized to 4-(*Z*) at 138° (refluxing *p*-xylene, $t_{1/2}$ ~50 min), and it was found that the isomerization of 3-(*E*) (mp 98°) was acid catalyzed, with 1 equiv of boron trifluoride etherate in benzene effecting the conversion to 3-(*Z*) at room temperature. Finally, the *E* geometry of 3-(*E*) and 4-(*E*) has been confirmed by single-crystal x-ray diffraction studies.[17]

Decoupling experiments on 1-(*E*) and 1-(*Z*) established that the lower field methine proton was coupled with the lower field methyl group doublet in each compound, a result which was duplicated with 1-(*E*) in the presence of $Eu(DPM)_3$. Further, the order of Lewis basicity toward $Eu(DPM)_3$ is 1-(*E*) > 1-(*Z*) ≫ **2** and, in fact, a threefold excess of 1-(*Z*) over 1-(*E*) was required before successful competition of the 1-(*Z*) isomer for a limited amount of $Eu(DPM)_3$ became evident. Also, since the proximal protons of **1** experienced the greater deshielding, the coordination site of $Eu(DPM)_3$ would appear to be the azoxy oxygen atom, rather than the distal N atom for this compound.

The chemical shifts of compounds **1**–**4** are recorded in Table II. A recent theoretical analysis[18] of azoxyalkane proton chemical shifts has for the first time allowed intelligent rationalization of the rather complex interplay of factors, including molecular conformation, which operate to determine the chemical shift of a given proton. At present,

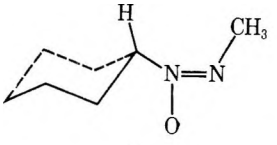
Table II. NMR Proton Chemical Shifts (δ) for Compounds 1–4

Entry	Compd	Solvent	Proximal[a]		Distal[a]	
			α	β	α	β
1	1-(*Z*)	CCl_4	4.38[b]	1.42[b]	4.12	1.11
2	1-(*E*)	C_6H_6	4.33	1.22	4.29	1.18
3	1-(*E*)	CCl_4	4.96	1.41	4.10	1.25
4	**2**	CCl_4	2.15[c]	1.13[c]		
5	**2**	CD_3COCD_3	2.19	1.13 1.10[d]		
6	**2**	C_6H_6	2.25	1.15 0.98[d]		
7	3-(*Z*)	$CDCl_3$	4.14[e]		3.10[f]	
8	3-(*Z*)	C_6D_6	4.12		3.16	
9	3-(*E*)	$CDCl_3$	4.55		3.51	
10	3-(*E*)	C_6D_6	4.19		3.02	
11	4-(*Z*)	$CDCl_3$	4.02		3.98	
12	4-(*Z*)	C_6D_6	3.51		4.14	
13	4-(*E*)	$CDCl_3$	4.16		3.60	
14	4-(*E*)	C_6D_6	3.49		3.05	

[a] Defined as follows: proximal-HC_β—HC_α—N(O)=N—CH_α—CH_β. [b] H-α's of **1** were symmetrical septets, J = 6.5 Hz, and H-β's were doublets. J = 6.5 Hz. [c] Little or no effect was seen with 0.06 equiv of $Eu(DPM)_3$ added. [d] Two doublets were observed for the β-CH_3 groups (see text). [e] Signals for methine hydrogens of **3** and **4** were broad, unresolved multiplets. [f] Signals for methyl group hydrogens of **3** and **4** were singlets.

about all that can be reliably predicted, however, is that a given proton situated above the plane of an azoxy functional group will be shielded relative to that same proton in the plane of the azoxy group.[5e,19] Some unusual facets of azoxyalkane proton chemical shifts have already been noted.[20] Also puzzling is that, in $CDCl_3$, a substantial downfield shift is observed for all protons upon *Z* to *E* isomerization, *except* for the distal α-H of **4**, which is shifted upfield (compare entry 7 with 9, and entry 11 with 13, Table II).

If the solid state conformations **6** and **7**[17] are used as solution models for 3-(*E*) and 4-(*E*), respectively, then the



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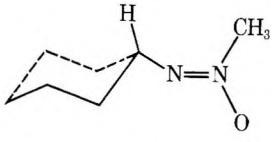

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benzene-induced shifts of the resonances of **3** and **4** are consistent with Williams' generalizations[21] about such phenomena. Thus, in the *Z* isomers the benzene solvent shifts the proximal H signals upfield while the distal H signals move downfield (compare entry 7 with 8 and entry 11 with 12, Table II). With the *E* isomers the signals for both proximal and distal protons are shifted upfield (compare entry 9 with 10 and entry 13 with 14, Table II). According to Williams, the benzene solvent molecule will probably be oriented in a nonplanar collision complex with the positive charge of a local dipole in such a fashion that the benzene ring lies away from the negative end of the dipole. With the aid of molecular models, Williams' generalizations are plausibly applied to the present cases. The steric bulk of the C_6H_{11} group of 3-(*Z*) produces a looser association with benzene than does the $CH_3N(O)$ grouping of 4-(*Z*). Hence, the solvent-induced shifts in 3-(*Z*) (in both directions) are of smaller magnitude. Also, models suggest that the distal protons of the *Z* isomers would, at a given moment, be located near the deshielding region of an associated benzene molecule. The *E* isomers, with their stronger dipole moment, form a stronger association complex with benzene. The geometry change apparently moves (and molecular

Table III. First-Order Rate Constants for the Thermal Rearrangement of Oxadiaziridine 5

Solvent	E_T[a]	ϵ[b]	Temp, °C	$k \times 10^{-4}$, sec^{-1} [c]	$t_{1/2}$, min
CD_3OD	55.5	32.6	40.5	6.71 ± 0.34[d]	18
			30.0	1.56 ± 0.14	75
			21.0	0.52 ± 0.11[d]	229
CD_3CN	46.0	36.2	40.5	6.10 ± 0.12	19
			21.0	0.68 ± 0.07[d]	173
C_6H_6	34.5	2.28	40.5	4.78 ± 0.19	24
CCl_4	32.5	2.23	40.5	3.03 ± 0.05	38
			21.0	0.26	446

[a] Reference 22. [b] Reference 23. [c] Average of two runs unless otherwise noted; uncertainties shown as standard errors, S_m. [d] Average of three runs.

models suggest this, also) the distal alkyl group to a position more directly above the benzene ring plane and into the shielding region of the benzene molecule in the complex. The steric effect of the $C_6H_{11}N(O)$ grouping is still evident, however, in that 3-(*E*) experiences smaller solvent shifts than does 4-(*E*).

Thermal Ring Opening of Oxadiaziridines. The thermal ring opening of oxadiaziridine 2 in several solvents has been reported by us previously.[5d] At that time it was noted that solvents of higher dielectric constant enhanced the yield of 1-(*E*), the more polar product, but with the best yield, the *E* isomer was still the minor product at 33%. Also, solvents of higher polarity caused a modest enhancement of the rate of ring opening.

With the unsymmetrically substituted oxadiaziridine **5** we have studied the kinetics of the ring-opening reaction in several solvents and have made an analysis of the products formed. It was our hope to be able to accurately monitor the rate of disappearance of the distinctive methyl NMR singlet of oxadiaziridine **5** and also accurately measure, by means of methyl singlet integration, the ratios of the product azoxyalkanes. However, as can be seen from Table II, there is overlapping of methine and methyl signals which complicated the analysis of product ratios [e.g., the proximal methine H of 3-(*Z*) and proximal CH_3 of 4-(*E*) have nearly the same chemical shift in $CDCl_3$ (entries 7 and 13, Table II)]. We took advantage of the substantial solvent-induced signal shifts observed for these compounds and arrived at an optimal method of employing a mixed solvent of benzene and the reaction solvent in a 3:1 by volume ratio for NMR analysis. However, even under these conditions, the broad absorption of the distal methine H of 4-(*E*) came underneath the CH_3 group absorptions of 3-(*Z*) and 3-(*E*). This necessitated the use of a correction factor, approximated by subtracting ⅓ of the integration value of the proximal methyl singlet of 4-(*E*) from the total integration of the 3-(*Z*) and 3-(*E*) methyl singlets. The ratio of **3/4** thus calculated tallied with that same ratio determined by VPC analysis under conditions which isomerized both *E* azoxyalkanes to their *Z* counterparts. However, we were not able to measure the product ratios as accurately as we desired, and accordingly have approached the interpretation of these results with some caution.

The rate constants determined in four solvents for the disappearance of **5** are collected in Table III. Qualitatively, the rate of ring opening is dependent upon the solvent parameter, E_T[22], not the dielectric constant of the solvent. The rate constants determined in CCl_4 at 21° showed an unexplained, systematic drift to lower value as the reaction progressed. The measurements made at the higher temperature were better behaved. The data collected at three temperatures in CD_3OD allowed the calculation of the activation parameters for the ring-opening reaction: E_a = 24.1 ± 0.3 kcal mol^{-1}; $\Delta H^{\ddagger}$ = 23.5 kcal mol^{-1}; $\Delta S^{\ddagger}$ = 1 ± 0.5 eu; $\Delta G^{\ddagger}_{30°}$ = 23.1 kcal mol^{-1}. As such, the parameters are comparable to those obtained for the ring opening of the somewhat more stable oxaziridine ring system: $\Delta H^{\ddagger}$ = 28 kcal mol^{-1}; $\Delta S^{\ddagger}$ = −3 ± 1 eu.[24]

The product yields obtained from the ring-opening reactions in the four same solvents are collected in Table IV

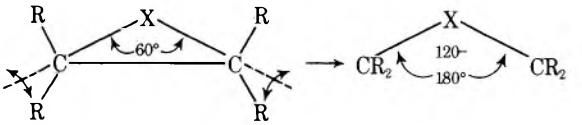
Table IV. Average Product Distributions[a] from Thermal Rearrangements of Oxadiaziridine 5 in Four Solvents

Solvent	Temp, °C	3-(*Z*), %	3-(*E*), %	4-(*Z*), %	4-(*E*), %
CD_3OD	40.5[b]	46	17	22	15
	21.0	45	18	21	15
CD_3CN	40.5	50	15	23	13
	21.0	48	18	20	13
C_6H_6	40.5	47	15	23	15
	21.0	51	15	21	12
CCl_4	40.5	51	16	22	10
	21.0	55	15	21	9

[a] Average of two runs unless otherwise noted; average deviation ±1%. [b] Average of three runs.

and various product ratios which were calculated are presented in Table V. From Table IV it can be seen that as the solvent polarity, as measured by its E_T value, is decreased from CH_3OH to CCl_4 the yield of the least polar product, 3-(*Z*), increases, principally at the expense of the most polar product, 4-(*E*). In Table V two of the ratios listed are of synthetic interest. Since we are able, by N–N bond synthesis, to prepare azoxyalkane 3-(*Z*) in good yield,[19] the oxygen migration effected by thermolysis of oxadiaziridine **5** would extend the utility of that synthesis. In this regard, the most favorable "**3/4**" ratios are obtained in methanol and, somewhat surprisingly, benzene (at 21°). Regarding the formation of *E* azoxyalkanes, in the event of an unfavorable *Z*–*E* photoequilibrium, thermolysis of the requisite oxadiaziridine can yield an *E* azoxyalkane as was noted previously.[5d] More polar solvents favor the formation of *E* azoxyalkanes as noted previously,[5d] and also as noted by the "*Z*/*E*" ratios of Table V. Again, benzene is seen to behave like a more polar solvent.

In ring-opening reactions of three-membered rings, the steric effects accompanying the rotatory motion of the terminal substituents play an important role in the outcome of such a reaction. Well known are the effects caused by various degrees and orientations of alkyl substitution on the ring-opening reaction of cyclopropyl tosylates and halides[25] (structure 8, X = CH^+). Less well known are the ste-



8

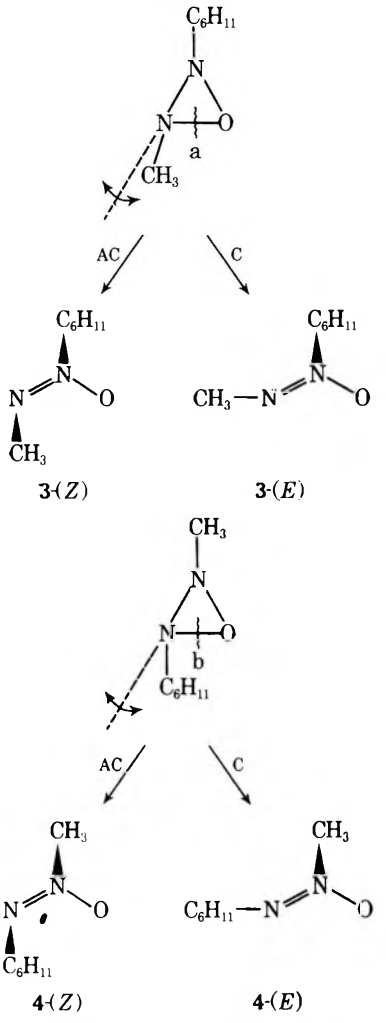
ric influences attending the ring opening of cyclopropylidines (8, X = C:). Thus, with trialkyl substitution on 8 (X = C:), monorotatory ring opening gives allenes as the only reaction products. With tetraalkyl substitution on 8 (X = C:), the ring-opening reaction is completely suppressed (CH insertion occurs), as result attributable to restriction of the rotatory motion of a CR_2 group.[26] Similarly, while substituent electronic effects can influence cyclopropylidine ring opening,[26c,27] the dominant effect is steric in the formation of optically active allenes.[27]

In a similar vein, analysis of the remaining product ratios of Table V indicates that steric effects play a more important role than electronic effects in the ring opening of **5**. Thus, with the aid of Scheme I, the ring opening of **5** can be considered a monorotatory process. Cleavage of N–O bond

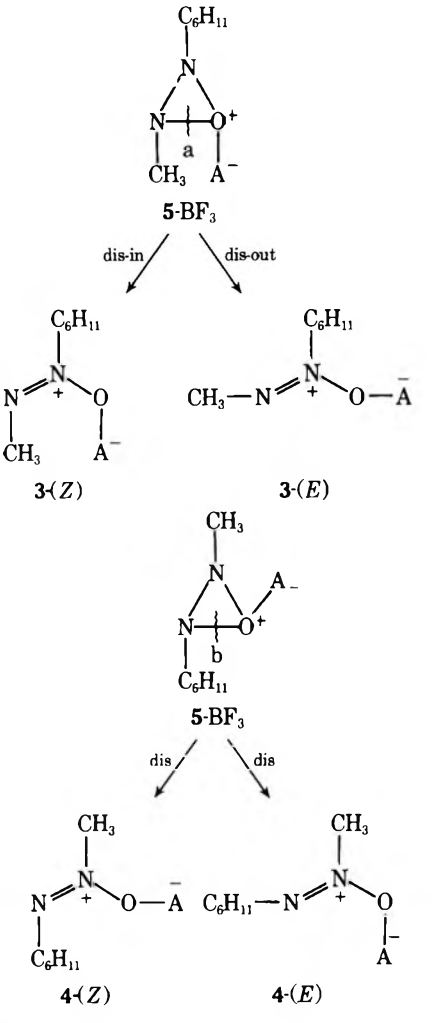
Table V. Product Ratios Obtained from Thermal Rearrangement of Oxadiaziridine 5

Solvent	Temp, °C	3/4	Z/E	3-(Z)/3-(E)	4-(Z)/4-(E)	3-(E)/4-(E)	3-(Z)/4-(Z)
CD_3OD	40.5	1.7	2.1	2.7	1.5	1.1	2.1
	21.0	1.7	2.0	2.5	1.4	1.2	2.1
CD_3CN	40.5	1.8	2.6	3.3	1.8	1.2	2.2
	21.0	2.0	2.2	2.7	1.5	1.4	2.4
C_6H_6	40.5	1.6	2.3	3.1	1.5	1.0	2.0
	21.0	2.0	2.7	3.4	1.7	1.2	2.4
CCl_4	40.5	2.1	2.8	3.2	2.2	1.6	2.3
	21.0	2.3	3.2	3.7	2.3	1.7	2.6

Scheme I



Scheme II[a]



[a] A = BF_3.

a of 5 yields 3 while cleavage of N–O bond b yields products 4. With cleavage of a, anticlockwise (AC) or clockwise (C) rotation of NCH_3 gives 3-(Z) or 3-(E), respectively. Likewise, with cleavage of b AC rotation of NC_6H_{11} gives 4-(Z), and C rotation gives 4-(E). With bond a cleavage, the rotating CH_3 group "confronts" groups of rather dissimilar size, C_6H_{11} vs. O; in contrast, with bond b cleavage the rotating C_6H_{11} group "confronts" groups of more similar size, CH_3 vs. O. The result is that the 3-(Z)/3-(E) ratio is always greater than the 4-(Z)/4-(E) ratio by close to a factor of 2 (CCl_4 solvent excepted).

The data of Table V permit a first estimate of the importance of substituent electronic effects on the ring opening. If we compare the two clockwise ring openings of 5 we see that in both instances, the CH_3 and C_6H_{11} groups confront each other. Thus, the steric effects in these two reactions should be about the same. Examination of the 3-(E)/4-(E) ratios in Table V indicates a modest preference for the formation of the $C_6H_{11}N(O)$ moiety, wherein the better electron-donating group (Taft σ^* for C_6H_{11} −0.15) is bound to the (formally) positively charged N. By contrast, the relative greater importance of steric effects can be gauged by comparing the two anticlockwise ring openings wherein C_6H_{11} and CH_3 "rotate against" the same group, oxygen. Thus the 3-(Z)/4-(Z) ratios in Table V exceed 2.

In summary, the relative yields of the four products can be explained principally on the basis of steric effects on the ring opening. Solvent effects alter the percentages of the products but do not change the order: 3-(Z) > 4-(Z) > 3-(E) > 4-(E). Substituent electronic effects may determine the relative yields of the last two compounds.

Acid-Catalyzed Ring Openings of Oxadiaziridines. Both acetic acid and $AgBF_4$ (1 equiv of each) accelerated the ring opening of 2 but did not materially affect the Z–E ratio of products as measured by NMR spectroscopy. With 5, 1 equiv of acid was required for efficient catalysis to open the ring, but also, 1 equiv of BF_3 was seen to effect the E to Z isomerization of 3 and 4. Thus, the E compounds formed by ring opening were isomerized prior to analysis of this reaction and only the 3-(Z)/4-(Z) ratio was measured. The results are presented in Table VI. A sub-

Table VI. Acid-Catalyzed Ring Opening of Oxadiaziridine 5 in Benzene at 20°

Acid	Molar ratio acid:5	Products[a] 3-(Z), %	4-(Z), %
CH_3CO_2H	1:1	67	33
CH_3CO_2H	4:1	72	28
$BF_3 \cdot OEt_2$	1:1	65	35
$BF_3 \cdot OEt_2$	4:1	49	51

[a] The yields, determined by VPC, represent the sum of E and Z isomers formed in the ring opening.

stantial increase in the more polar products 4 is evident when the ring opening is conducted in the presence of an excess of an acid with bulk sufficient to impart steric effects to its acid–base reactions. It is interesting to note that the increase of 4 is consistent with the intervention of a disrotatory opening of the (probable) preferred conjugate acid of 5. Thus, as Scheme II illustrates, coordination of BF_3 with 5 at oxygen should occur preferentially syn to the less bulky CH_3 group.[28] Cleavage of bond a with dis-in motions of the NCH_3 and O–A groups leads to an unfavorable CH_3–A interaction on the pathway to 3-(Z) congutate acid. Thus, with a restriction placed on the pathway to the major azoxyalkane, 3-(Z), and with no similar restriction placed on the pathway to 4-(Z), the 3/4 ratio, normally 1.7 or greater, could be decreased.[31] Since the azoxyalkanes are recoverable in good yield from these reactions, the acid-catalyzed ring opening of oxadiaziridines holds some synthetic promise for effecting the N to N′ oxygen transfer reaction.

Experimental Section

General. For instruments used, see the Experimental Section of ref 20b. Photochemical reactions were performed in a nitrogen atmosphere using either a medium-pressure 450-W Hanovia type L lamp (lamp H) or a Rayonet photochemical reactor, Model RPR-100 (lamp R) equipped with a 16-tube, variable light source with 350, 300, or 254 nm as the principal emission wavelength choices. Cooling of certain photolysis reactions was accomplished by circulating an externally cooled coolant (usually methanol) around the appropriate immersion well.

VPC columns of aluminum tubing (0.125 and 0.25 in. o.d.) packed with the following adsorbants were used: column A, 5% Carbowax 20M on Anakrom or Chromosorb W (AW and DMCS); B, 5% UCW-98 on Diatoport S; C, 10–20% Carbowax 20M on Chromosorb W (AW and DMCS); D, 20% SE-30 on Anakrom; E, 20% Dow 710 silicone oil on Chromosorb W (AW and DMCS); F, 3 ft × 0.25 in. 20% Dow 710 silicone oil on Chromosorb W (AW and DMCS); G, 10 ft × 0.25 in. 20% SE-30 on Chromosorb W (AW and DMCS).

(Z)-Bis(1-methylethyl)diazene.[32] Thirty-six grams of (E)-bis-(1-methylethyl)diazene[33] was irradiated (lamp R, 350 nm) in a water-cooled Pyrex immersion well for 15–24 h, at which time VPC analysis (column G) indicated 4–7% conversion to the Z isomer. Distillation (760 nm) concentrated the desired Z isomer in the 4-g residue (~40% Z). Repetition of this photolysis–distillation sequence seven times gave 14.8 g of concentrates with 13.8 g of distilled E isomer remaining. Spinning band distillation of the concentrates (60° pot temperature, 80 nm) gave pure E as the distillate and continued distillation with gradual reduction in pressure (to 10 nm) gave 3.94 g of Z isomer (99% purity by VPC analysis, column G): uv λ_{max} 373 nm (ϵ 103); NMR (CCl_4) δ 1.23 (d, J = 7 Hz, CH_3), 4.05 (septet, J = 7 Hz, CH); the foregoing spectral data were in agreement with literature[32] values.

(E)-Bis(1-methylethyl)diazene Oxide [1-(E)]. A saturated solution of 5.62 g (0.027 mol) of m-chloroperoxybenzoic acid in 30 ml of CH_2Cl_2 was added to a stirred solution of 3.0 g (0.026 mol) of (Z)-bis(1 methylethyl)diazene in 10 ml of CH_2Cl_2 at 0°. After 2 h at 0° the reaction mixture was stirred for 1 h at room temperature, then quenched by the rapid sequential addition of 10 ml of 10% aqueous potassium iodide and 15 ml of 10% aqueous sodium thiosulfate. The organic phase was washed with 20 ml of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. NMR analysis of the residue showed the presence of a minor amount of m-chlorobenzoic acid. Column chromatography over 50 g of silica gel using CH_2Cl_2–ether, 10:1 by volume, as eluent and taking 30-ml fractions yielded 2.46 g (72%) of 1-(E) in fractions 5, 6, and 7. Preparative VPC (column E) using the following conditions gave an analytical sample (thermal conductivity detector temperature 150°; column temperature 105°; injection port temperature 150°; carrier gas 200 ml/min): ir (CCl_4) 1480 and 1275 cm^{-1}; uv (EtOH) λ_{max} 232 nm (ϵ 7900); NMR, see Table II.

Anal. Calcd for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.53. Found: C, 55.34; H, 10.83; N, 21.76.

(E)-2,3-Bis(1-methylethyl)oxadiaziridine (2). A solution of 22 g (0.17 mol) of 1-(Z)[34] in 240 ml of pentane was irradiated (lamp H, Vycor filter) in a water-cooled (10°) quartz immersion well for 17 h. VPC analysis (column E, injection port temperature 80°; temperature program rate 4 min at room temperature, then 8°/min to 120°) indicated the presence of 2 (52%), 1-(Z) (20%), and 28% of other compounds including (E)- and (Z)-bis(1-methylethyl)diazene and 1-(E). A 50-ml aliquot of the mixture was distilled in vacuo (13°, 190 mm) to remove the pentane solvent, and then at 40° (190–25 mm) to yield 1 g of distillate containing equal amounts of 1-(Z) and 2. The distillate was chromatographed over 10 g of silica gel at less than 10° eluting with pentane to give 107 mg of 2 of about 98% purity after distillation of the solvent in vacuo (−20°, 15 mm). An additional 85 mg of 2 was recovered by redistillation of the solvent at −40° (1 mm).

Using a more careful control of temperature and pressure during distillation allowed the isolation of 2 directly from the reaction mixture in 38% yield with purity of about 85%.

Preparative VPC (column F, injection port temperature 80°, column temperature 25°, thermal conductivity detector temperature 85°; carrier gas 200 ml/min) allowed the isolation of pure 2 with less than 1% isomerization to 1-(Z): NMR, see Table II.

Small-Scale Photolyses of 1-(Z) and 1-(E). Solutions containing 50 or 100 mg of 1 at 0.5–1% concentration by volume were irradiated, and the reactions were monitored by VPC analysis (column B, injection port temperature 80°). The results are summarized in Table VII.

Table VII. Small-Scale Photolysis Results for Compounds 1-(Z) and 1-(E)

Compd (solvent)	Conditions: lamp (nm), filter	Time, hr	Products, % 1-(Z)	1-(E)	2
1-(Z) (neat)	R (350), Pyrex	12	100		
1-(Z) (C_6H_{12})[a]	H, quartz, Vycor	2	94		6
		6	84		16
		16	70		25
1-(Z) ($CHCl_3$)[a]	H, quartz, Vycor	2	96		4
		6	89		11
		9.5	83		17
		16.5	77		22
1-(E) (C_6H_{12})	R (350), Pyrex	16	97	3	
1-(E) (C_5H_{12})[a]	H, quartz, Vycor	2	61	39	
		5	86	7	7
		8	82	2	16

[a] Reaction cooled at 10°.

Small-Scale Photolyses of 3-(Z) and 4-(Z). Solutions containing 50 to 100 mg of 3-(Z) or 4-(Z) at about 10% concentration by volume were irradiated with lamp H in quartz NMR tubes suspended inside a quartz immersion well which was cooled and fitted with a Vycor filter sleeve. The product ratios were analyzed by NMR spectroscopy (NCH_3 signal integration) and by isolation. The results are summerized in Table VIII.

(E)-Cyclohexylmethyldiazene 1-Oxide [3-(E)]. A solution of 2.5 g of 3-(Z)[19] in 250 ml of pentane was irradiated (lamp H, Vycor filter) in a quartz immersion well at −30° for 2.5 h. The solid which separated was collected by filtration to give 0.77 g (31%) of a mixture of 3-(E) and 4-(E) in a ratio of 12, mp 95–96°. Recrystallization of the solid from benzene–hexane gave 3-(E) of 97% purity [3% 4-(E)]. An analytical sample, mp 98.5°, was obtained by preparative VPC (column D, injection port temperature 135°, column temperature 120°, thermal conductivity detector temperature 125°): ir (KBr) 1500 and 1304 cm^{-1}; uv (EtOH) λ_{max} 232 nm (ϵ 5900); NMR, Table II.

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92. Found: C, 58.92; H, 10.20.

(E)-2-Cyclohexyl-3-methyloxadiaziridine (5). The filtrate from the preceding experiment was concentrated at −30° (2.5

Table VIII. Small-Scale Photolysis Results for Compounds 3-(*Z*) and 4-(*Z*)

Compd (solvent)	Temp, °C	Time, hr	Products, %[a]				
			3-(*Z*)	3-(*E*)	4-(*Z*)	4-(*E*)	5
3-(*Z*) (CD_3OD)	−15	7.5	87	12			Trace
3-(*Z*) (C_5H_{12})	−15	6	93	5[b]			2
4-(*Z*) (CD_3OD)	−25	2.5			98[c]	*c*	2
4-(*Z*) (C_5H_{12})	−25	6			65	31[b]	4

[a] Determined by NMR analysis unless otherwise noted. [b] Isolated yield. [c] In CD_3OD the NCH_3 signals of 4-(*Z*) and 4-(*E*) nearly coincide, making a ratio determination impossible. This experiment predated the knowledge of the utility of the benzene solvent induced shift technique used in the analysis of the rearrangement of 5.

mm), thereby removing the pentane solvent. Further distillation at −20° (0.5 mm) gave 0.68 g (27%) of **5**, NMR ($CDCl_3$) δ 2.60 (s, NCH_3).

The distillation residue, 0.95 g (38%), a mixture of 3-(*Z*) and 4-(*Z*) in a ratio of 6.7, was analyzed by NMR spectroscopy and checked by VPC analysis.

(*E*)-Methylcyclohexyldiazene 1-Oxide [4-(*E*)]. A solution of 3.3 g of 4-(*Z*)[19] in 310 ml of pentane was irradiated (lamp H, Vycor filter) in a quartz immersion well at −30° for 2.5 h. The solid which separated was collected by filtration to give 0.63 g (18%) of nearly pure 4-(*E*), mp 138–140°. Recrystallization from benzene–hexane gave an analytical sample: mp 140–141°; ir ($CHCl_3$) 1500 and 1306 cm^{-1}; uv (EtOH) λ_{max} 233 nm (ε 8000); NMR, Table II.

Anal. Calcd for $C_7H_{14}N_2O$: C, 59,13; H, 9.92. Found: C, 59.39; H, 10.20.

Alternate Preparation of Oxadiaziridine 5. The filtrate from the preceding experiment was concentrated in vacuo at −30° and then chromotographed at −10° over 50 g of silica gel. Elution with 800 ml of 20% CH_2Cl_2 in pentane gave **5** as the first compound off the column. Cold evaporation of the solvent gave 1.89 g (58%) of **5**. Continued elution with 200 ml of CH_2Cl_2 gave 0.44 g (13%) which was principally a mixture of 4-(*Z*) and 3-(*Z*) in a ratio of 1.2. This fraction also contained a small amount of an unknown, presumed to be cyclohexylmethyldiazene as evidenced by a singlet at δ 3.8 in the NMR spectrum of the mixture. (The NCH_3 signal of phenylmethyldiazene occurs at δ 3.9, and that of dimethyldiazene at δ 3.8.)

Thermal Isomerization of 4-(*E*). A solution of 22.0 mg of 4-(*E*) in 0.25 ml of benzene was sealed under nitrogen. The tube was heated in refluxing xylene (138°) and periodically monitored by NMR analysis. At 2 h 40 min, the spectrum had changed from that of 4-(*E*) to that of 4-(*Z*). At 50 min, the NCH_3 signals were approximately of equal intensity.

Thermal Isomerizations of 5. Solutions of 10.0–20.0 μl of **5** in 0.3 ml of solvent were placed in a nitrogen-flushed NMR tube cooled to −80°. To this a known amount (~10 mg) of CH_2Cl_2 was added as internal standard. The initial amount of **5** was estimated by integrating the methyl signal of **5** and CH_2Cl_2. For the rearrangements at 40.5°, the reactions were conducted in the NMR instrument probe and the rate of disappearance of the methyl signal with respect to CH_2Cl_2 was monitored for 3 or 4 half-lives. For rearrangements at the other temperatures, the NMR probe was cooled to the appropriate temperature for the measurements, but the reaction was conducted in a constant-temperature bath. Normally, 8–16 readings were taken in a given experiment and the first-order rate constant obtained by the least-squares method. E_a was calculated, in turn, from the least-squares line of a plot of $1/T$ vs. log k using the eight rate constants obtained in CD_3OD solvent; for $\Delta H^{\ddagger}$ the approximation $\Delta H^{\ddagger} = E_a - RT$ was used (T = 303°); $\Delta S^{\ddagger}$ was calculated from log A (13.6 sec^{-1}). The kinetic data are summarized in Table III. For analysis of product ratios, the sample tube was opened, benzene was added, and the methyl signals reintegrated using the correction noted in the text. When benzene was the solvent, bromobenzene was added to spread the methyl signals of 4. Periodic VPC analysis of single runs (column A) was used to check the integration results; for example, in CCl_4 (21°) **3/4** = 2.25 by NMR, 2.31 by VPC; in CD_3OD (21°) **3/4** = 1.78 by NMR, 1.91 by VPC; in CD_3CN (21°) **3/4** = 1.88 by NMR, 1.97 by VPC. Product distribution data are collected in Table IV.

Acid-Catalyzed Isomerization of 5. The acid used was added to a cold (15°) solution of ~50 μl of **5** in 1.5 ml of benzene under a nitrogen atmosphere. The density of **5** was assumed to be 1 for purposes of measuring the appropriate molar ratio of acid. After 12 h of stirring at 15–20° the acid was neutralized by the addition of a slight excess of pyridine. (With BF_3, the resulting complex precipitated and was removed by filtration.) A quantitative analysis of the product ratios was made by VPC (column C) under conditions assured to isomerize both *E* isomers. The results are summarized in Table VI. In separate experiments, 1 equiv of boron trifluoride etherate in benzene was seen to effect the isomerization of 3-(*E*) to 3-(*Z*) as evidenced by NMR spectroscopy, and 3-(*Z*) was shown to be stable in the presence of 4 equiv of boron trifluoride etherate as evidenced by VPC analysis (column C).

Registry No.—1-(*Z*), 35216-94-5; 1-(*E*), 35216-96-7; **2**, 57497-44-6; 3-(*Z*), 35214-91-6; 3-(*E*), 35214-90-5; 4-(*Z*), 57497-35-5; 4-(*E*), 57497-45-7; **5**, 57497-46-8; (*Z*)-bis(1-methylethyl)diazene, 23201-84-5; (*E*)-bis(1-methylethyl)diazene, 15464-00-3.

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Crystal and Molecular Structure of Bis(dimethylphosphatovinyl) Carbonate ($C_9H_{16}P_2O_{11}$)

Mazhar-Ul-Haque,[1a] Charles N. Caughlan,*[1a] G. David Smith, Fausto Ramirez,[1b] and Stephen L. Glaser

Departments of Chemistry, Montana State University, Bozeman, Montana 59715, and State University of New York at Stony Brook, Stony Brook, New York 11794

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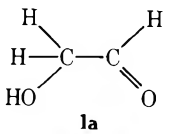
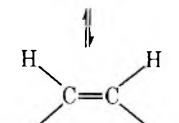
The reaction of 2 mol of 2,2,2-trimethoxy-2,2-dihydro-1,3,2-dioxaphospholene with 1 mol of phosgene ($COCl_2$) gave bis(dimethylphosphatovinyl) carbonate, $C_9H_{16}P_2O_{11}$. The crystal structure of this vinyl phosphate–vinyl carbonate was solved by x-ray diffraction techniques. The crystals grow in an orthorhombic space group *Pbca* with eight molecules per unit cell. The cell dimensions are a = 7.257 (2), b = 21.788 (8), and c = 20.267 (8) Å. Intensities of 1415 reflections were measured on a G.E. XRD-5 diffractometer. The structure was solved by Patterson methods and refined to a final R of 9.5% for 912 observed reflections by least-squares methods. Bond angles around both phosphorus atoms deviate from those of a tetrahedron, ranging from 99.4 to 116.9° and 101.3 to 115.4°, respectively. The formation of a trigonal bipyramidal oxyphosphorane intermediate by the addition of nucleophiles to the phosphorus involves relatively small additional bond angle deformations.

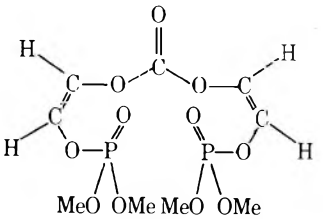
This paper describes the synthesis and the crystal and molecular structure of a carbonate–diphosphate ester, **2**, derived from the enediol tautomer, **1b**, of glycolaldehyde.



1a



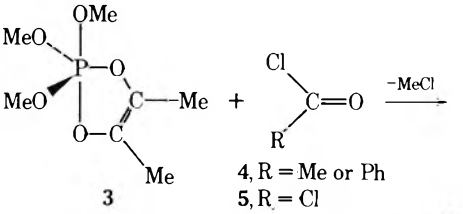
1b



2

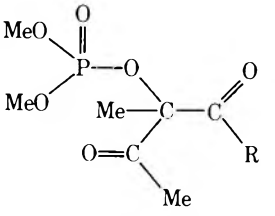
There is now considerable information on the molecular structure and the reactivity of five-membered cyclic unsaturated[2] and saturated[3-7] phosphate esters and phosphate esters of hydroxy ketones.[8,9] The x-ray structure of methyl ethylene phosphate[10] and methyl pinacol phosphate[11] have been described.

Synthesis of Bis(dimethylphosphatovinyl) Carbonate (2). The synthesis of the carbonate **2** is based on a remarkable property of the 2,2,2-trialkoxy-1,3,2-dioxaphospholene system,[12] **3**, with pentacoordinated phosphorus. According to x-ray crystallographic data, the ring in five-membered[13-17] and four-membered[18] cyclic oxyphosphoranes occupies the apical equatorial skeletal position in a trigonal bipyramid. The oxyphosphorane **3** *with two methyl substituents on the ring* undergoes exclusive C-acylation[19] with acyl halides **4** and with phosgene (**5**) under certain conditions, to give phosphate esters of α-hydroxy-β-diketones, **6**, and of α-hydroxy-β-keto acid chlorides, **7**, respectively. In contrast, the oxyphosphorane **8** *with hydrogens on the ring* undergoes exclusive O-acylation[20] under comparable conditions, to give the carboxylate–phosphate

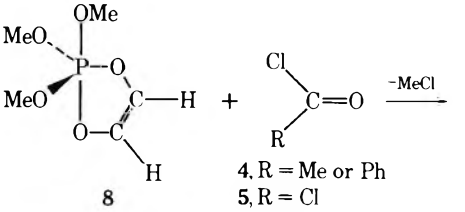


3

4, R = Me or Ph
5, R = Cl

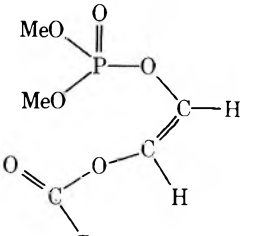


6, R = Me or Ph
7, R = Cl



8

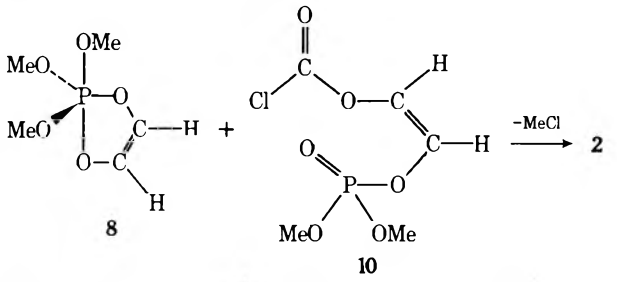
4, R = Me or Ph
5, R = Cl



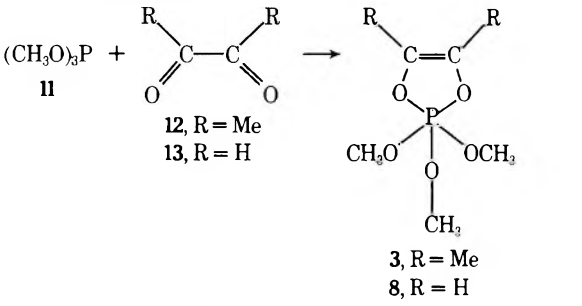
9, R = Me or Ph
10, R = Cl

ester derivatives **9** and **10** of the enediol tautomer of glycolaldehyde.

The chlorocarbonate–phosphate ester **10** reacts with a second mole of the oxyphosphorane, **8**, to give the desired crystalline carbonate **2**. The latter, **2**, can be made directly from the oxyphosphorane, **8**, and phosgene (**5**) without the isolation of the monophosphate **10**.



The oxyphosphoranes[12] **3** and **8** are synthesized from trimethyl phosphite (**11**) and the corresponding α-dicarbonyl compound, biacetyl (**12**) and glyoxal (**13**).



Experimental Section

Bis(dimethylphosphatovinyl) Carbonate (2). Phosgene ($COCl_2$) was passed through anhydrous $CuSO_4$, condensed in a calibrated trap at −70 °C, and distilled into a flask containing CH_2Cl_2 at 0 °C. A solution of 2,2,2-trimethoxy-2,2-dihydro-1,3,2-dioxaphospholene (**8**, 78.4 g, 2 molar equiv) in CH_2Cl_2 (30 ml) was added to the phosgene–CH_2Cl_2 solution at 0 °C. The addition lasted 15 min, and the reaction mixture was kept for 1 h at 0 °C and 2 h at 20 °C, with stirring. The solvent was removed at 30 °C and 20 mm (last traces at 0.2 mm), and the residue was recrystallized from benzene or from chloroform-ether. The bisphosphate **2** had mp 69–70 °C and was obtained in 95% yield: $\delta^{31}P$ +2.9; τ_A 3.65; τ_B 3.65; $J^A_{HC=CHB}$ = 3.5; $J^A_{HC=COP}$ = 1.2; J^B_{HCOP} = 5.9 Hz; τ_C 6.15; J^C_{HCOP} = 11.5 Hz.[28]

Anal. Calcd for $C_9H_{16}O_{11}P_2$: C, 29.8; H, 4.4; P, 17.1. Found: C, 29.6; H, 4.4; P, 17.0.

The bisphosphate **2** was also made in two stages. (1) The oxyphosphorane **8** (1 mol) in CH_2Cl_2 was added to phosgene ($COCl_2$, 1–2 mol) in CH_2Cl_2 at 0 °C (30 min). After 30 min at 20 °C, the solvent was removed and the dimethyl phosphatovinyl chlorocarbonate[20] (**10**) was purified by short-path distillation: bp 95–97 °C (0.5 mm); $\delta^{31}P$ −1.6; τ_A 3.33; τ_B 3.78; $J^A_{HC=CHB}$ = 3.5; $J^A_{HC=COP}$ = 1.1; J^B_{HCOP} = 5.9 Hz; τ_C 6.15; J^C_{HCOP} = 11.2 Hz.[28] (2) The oxyphosphorane **8** (1.1 mol) in CH_2Cl_2 was added to the chlorocarbonate **10** (1 mol) in CH_2Cl_2 at 0 °C. After 1 h at 20 °C, the solvent was removed and the bisphosphate **2** was purified as indicated above.

X-Ray Crystallographic Data. Crystals of the carbonate **2** were sealed in Lindemann glass capillaries under a dry argon atmosphere for x-ray examination. Preliminary Weissenberg and precession photographs indicated the orthorhombic space group *Pbca* with systematic absences: $0kl$, $k = 2n + 1$; $hk0$, $h = 2n + 1$; and $h0l$, $l = 2n + 1$. Lattice dimensions were determined from least-squares refinement of 20 2θ values measured on a G.E. XRD-5 diffractometer: a = 7.257 (2); b = 21.788 (8); and c = 20.267 (8) Å. The density was not measured but the calculated density is 1.499 g/cm^3 for eight molecules per unit cell. The linear absorption coefficient is 3.3 cm^{-1} for Mo Kα radiation.

The crystal used for collection of intensity data was 0.12 × 0.14 × 1.3 mm. The intensity data were collected with zirconium-filtered Mo Kα radiation on a G.E. diffractometer equipped with a scintillation counter for detection. The crystal decomposed in the x-ray beam, completely disappearing in about 10 days. Because of this, the data were collected by counting only peak heights. In order to bring the intensity data to a uniform scale, the intensities of three standard reflections were recorded every 2 h and used to scale the data. The background was estimated from a single scan from 3 to 45 °C.

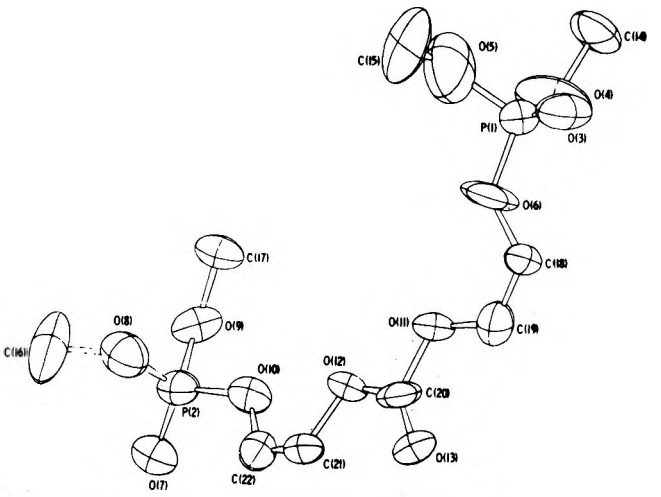


Figure 1. ORTEP drawing of bis(dimethylphosphatovinyl) carbonate ($C_9H_{16}P_2O_{11}$).

The intensities of 1415 reflections were measured in this way and 912 were considered above background by estimating $I > 3\sigma(I)$. The data were corrected for Lorentz and polarization factors.[21] Neither absorption nor extinction corrections were applied; however, both real and imaginary terms were used for the form factor of phosphorus. Form factors were taken from the International Tables for X-Ray Crystallography.[22]

Structure Determination and Refinement. The structure was solved from the three-dimensional Patterson by first locating the phosphorus positions from the Harker section. The Fourier synthesis phased on these atoms showed the oxygen atoms around the phosphorus atoms and the next Fourier synthesis showed the complete structure. Both positional and anisotropic thermal parameters were refined by full-matrix least squares, minimizing $\Sigma w|(F_o - F_c)|$.[2] Weights were calculated according to the method of Hughes,[23] since counting statistics were not considered valid, because of data collection difficulties; the final R factor ($R = \Sigma|F_o - F_d|/\Sigma F_o$) was 0.095. A final three-dimensional difference map showed no features >0.5 eA^{-3}. Hydrogen atom locations were not attempted.

Discussion

Figure 1 is an ORTEP drawing of the molecule while Table I lists the bond distances and angles.[24]

The large standard deviations for the bond distances and angles are mainly due to difficulties in the collections of data. The short carbon–oxygen distance of 1.17 Å for the carbonate is definitely shorter than the accepted value for CO_3^{-2} of 1.29 (4) Å.[25] However, it does compare favorably with that of $COCl_2$ (1.17 Å) and CO_2 (1.16 Å). The C=C distances of 1.29 Å are slightly shorter than the average value of 1.34 Å.[26]

The carbon atom, C(20), and three surrounding oxygen atoms of the carbonate group are planar, with deviations from the least-squares plane of 0.001 Å. The angles around C(20) vary from 106.9° to 127.2° even though the sum is 360°. This represents a considerable distortion from the normal 120° in the carbonate ion.[27] Inorganic carbonates show some variations from 120°, but not as large as these.

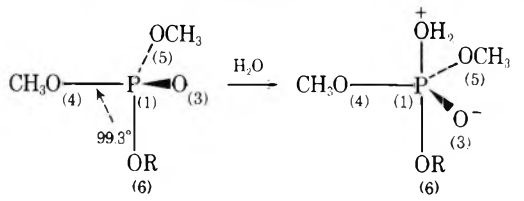
With respect to the phosphate groups, the sets of atoms O(3)–P(1)–O(6)–C(18) and O(7)–P(2)–O(9)–C(17) are nearly planar, with deviations from the least-squares planes of less than 0.1 and 0.02 Å, respectively. The other four O–P–O–C planes show considerably greater deviations.

One of the most interesting features of the structure of **2** pertains to the bond angles about the tetracoordinated

Table I. Bond Distances and Angles

P(1)–O(3)	1.42 (1)	P(2)–O(7)	1.42 (1)
P(1)–O(4)	1.56 (2)	P(2)–O(8)	1.58 (1)
P(1)–O(5)	1.57 (1)	P(2)–O(9)	1.56 (1)
P(1)–O(6)	1.54 (1)	P(2)–O(10)	1.56 (1)
O(4)–C(14)	1.43 (2)	O(8)–C(16)	1.46 (2)
O(5)–C(15)	1.36 (2)	O(9)–C(17)	1.45 (2)
O(6)–C(18)	1.41 (2)	O(10)–C(22)	1.35 (2)
C(18)–C(19)	1.29 (2)	C(21)–C(22)	1.29 (2)
O(11)–C(19)	1.40 (2)	O(12)–C(21)	1.38 (1)
O(11)–C(20)	1.37 (2)	O(12)–C(20)	1.36 (2)
		C(20)–O(13)	1.17 (2)
O(3)–P(1)–O(4)	115.7 (7)	O(7)–P(2)–O(8)	115.4 (6)
O(3)–P(1)–O(5)	116.9 (7)	O(7)–P(2)–O(9)	112.2 (6)
O(3)–P(1)–O(6)	115.0 (7)	O(7)–P(2)–O(10)	115.4 (6)
O(4)–P(1)–O(5)	103.9 (8)	O(8)–P(2)–O(9)	108.4 (5)
O(4)–P(1)–O(6)	99.4 (7)	O(8)–P(2)–O(10)	101.3 (5)
O(5)–P(1)–O(6)	103.7 (7)	O(9)–P(2)–O(10)	102.7 (5)
P(1)–O(4)–C(14)	123.7 (12)	P(2)–O(8)–C(16)	120.6 (10)
P(1)–O(5)–C(15)	127.9 (13)	P(2)–O(9)–C(17)	122.2 (8)
P(1)–O(6)–C(18)	122.8 (9)	P(2)–O(10)–C(22)	119.6 (9)
O(6)–C(18)–C(19)	117.3 (13)	O(10)–C(22)–C(21)	123.4 (13)
C(18)–C(19)–O(11)	121.4 (13)	C(22)–C(21)–O(12)	119.2 (13)
C(19)–O(11)–C(20)	116.7 (11)	C(21)–O(12)–C(20)	115.0 (10)
O(11)–C(20)–O(13)	125.9 (14)	O(12)–C(20)–O(13)	127.2 (14)
		O(11)–C(20)–O(12)	106.9 (11)

phosphorus atoms. These angles show significant departures from the tetrahedral 109° value, notably O(4)–P(1)–O(6) = 99.4°, O(5)–P(1)–O(6) = 103.7°, O(3)–P(1)–O(4) = 115.7°, for one of the phosphate functions and O(8)–P(2)–O(10) = 101.3°, O(9)–P(2)–O(10) = 102.7°, O(7)–P(2)–O(8) = 115.4°, for the other phosphate group. On the assumption that a trigonal bipyramidal oxyphosphorane is formed as an intermediate in nucleophilic displacement on tetracoordinated phosphorus,[2-9] the data show that only relatively small additional distortions of the O–P–O bond angles of **2** can lead to the trigonal bipyramid when water or hydroxide ion is added to the phosphorus.[12d]



14 (= **2**) **15**

Registry No.—**2**, 57775-18-5; **5**, 75-44-5; **8**, 5871-05-6; **10**, 57918-70-4.

Supplementary Material Available. Observed and calculated structure factors and a table of final positional and thermal parameters along with their standard deviations (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Montana State University. We (M.U.H., C.N.C.) acknowledge a grant from NIH, GM-08395-08, for partial support of this work. We are grateful to Montana State University for computing time. (b) State University of New York at Stony Brook. We (F.R. and S.L.G.) acknowledge the support of this work by Grant GM-20672 from the General Medical Institute of the NIH and Grant MPS-73-04944 from the National Science Foundation.
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(28) ^{31}P shifts in parts per million vs. H_3PO_4 = 0; in CH_2Cl_2, at 40.5 MHz. ^1H shifts in parts per million vs. Me_4Si 10 (τ), J in hertz; in $CDCl_3$ at 60 MHz.

X-Ray Analysis of *cis*-1-Iodomethyl-3-methyl-1-phenylphospholanium Iodide and Assignment of Configuration to Stereochemically Related Phospholane Derivatives

Alvin Fitzgerald, G. David Smith, and Charles N. Caughlan*

Department of Chemistry, Montana State University, Bozeman, Montana 59715

Kenneth L. Marsi and Frank B. Burns

Department of Chemistry, California State University, Long Beach, Long Beach, California 90840

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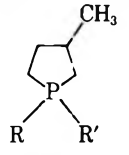
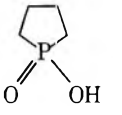
The crystal and molecular structure of the isomer of 1-iodomethyl-3-methyl-1-phenylphospholanium iodide of mp 192–193 °C (**1c**) has been determined by x-ray analysis and the methyl group found to be trans to the phenyl substituent. The phospholanium ring appears to be in the envelope form with the methyl group at the point of the flap. The crystals are monoclinic of space group $P2_1/c$ with a = 7.217 (3) Å, b = 14.261 (6) Å, and c = 14.778 (6) Å, β = 106.54 (3)°. The structure was solved from the three-dimensional Patterson function by location of the iodine positions and refined by using full-matrix least squares to an R factor of 4.5% for the observed data. Bond distances around phosphorus range from 1.78 (1) to 1.82 (1) Å while the endocyclic angle at phosphorus is 96.0 (4)°. The exocyclic angles at phosphorus average 112°. By the use of stereospecific reactions, the trans and cis configurations of isomers of the following constitution are now known: 3-methyl-1-phenylphospholane, 3-methyl-1-phenylphospholane 1-oxide, 1,3-dimethyl-1-phenylphospholanium bromide, 1-benzyl-3-methyl-1-phenylphospholanium bromide, 1-iodomethyl-3-methyl-1-phenylphospholanium iodide, 1-methoxy-3-methyl-1-phenylphospholanium hexafluorophosphate, 1,3-dimethylphospholane, 1,3-dimethylphospholane 1-oxide, and 1-benzyl-1,3-dimethylphospholanium bromide. The x-ray structure determination also reveals that catalytic addition of hydrogen to 3-methyl-1-phenyl-2-phospholene 1-oxide occurs stereospecifically to the oxide side of the phospholene ring.

Several reasons prompted this structural analysis of a derivative of 3-methyl-1-phenylphospholane (**1a**). We have chosen the isomer of 1-iodomethyl-3-methyl-1-phenylphospholanium iodide (**1c**) of mp 192–193 °C for this study because of its stability and the suitability of the crystals for x-ray analysis. Its configuration has been found to be cis.[1]



1a, R = Ph; R′ = lone pair
b, R = Me; R′ = lone pair
c, R = Ph; R′ = CH_2I



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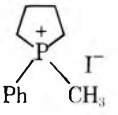

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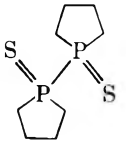

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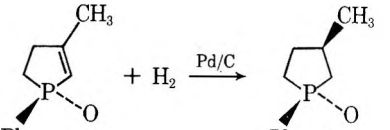
Although structure determinations for three compounds possessing simple phospholane rings (**2**,[2] **3**,[3] **4**[4]) are reported in the literature, none of these substances possess substituents on ring carbons, and thus the effect of substitution on ring structure has remained unknown.

One of us (K.L.M.) has participated in rather extensive investigations into the stereochemistry of nucleophilic substitution reactions at phosphorus in phospholane ring systems employing geometrically isomeric derivatives of **1a** and **1b**.[5] Although conclusions could be drawn concerning the stereochemistry of most reactions studied because of the completion of stereochemical cycles, the actual geometric configurations of the isomers used were unknown. Because of the similarity of ^1H NMR (60 MHz) and ^{31}P NMR (100 MHz) spectra of the trans and cis isomers of these phospholane derivatives, stereochemical assignments could not be made with confidence by NMR. During the course of these studies nine sets of geometrical isomers, structurally related to **1**, were prepared in analytical and isomeric purity and characterized. These are shown in Chart I together with their configurational assignments and certain physical properties. Their geometric configurations were determined by relating these compounds through reactions of known stereochemistry (Chart I) to the structure of *cis*-1-iodomethyl-3-methyl-1-phenylphospholanium iodide (**5**) whose crystal structure analysis is reported in this paper. Knowledge of the configurations of these compounds will also be useful in future stereochemical studies.

The x-ray structure determination of **5** has enabled us to assign stereochemistry to two reactions of previously undemonstrated stereochemistry. First, it has been noted that the reduction of 3-methyl-1-phenyl-2-phospholene 1-oxide[6] (**6**) with hydrogen in the presence of palladium on carbon catalyst yields only one of two possible diastereomers as a racemic mixture.[5d] This work has established the fact that addition of hydrogen occurs *exclusively from the oxygen side of the heterocycle* to yield the trans isomer (shown for one enantiomer in eq 1). It should be noted that



6 **7** (1)

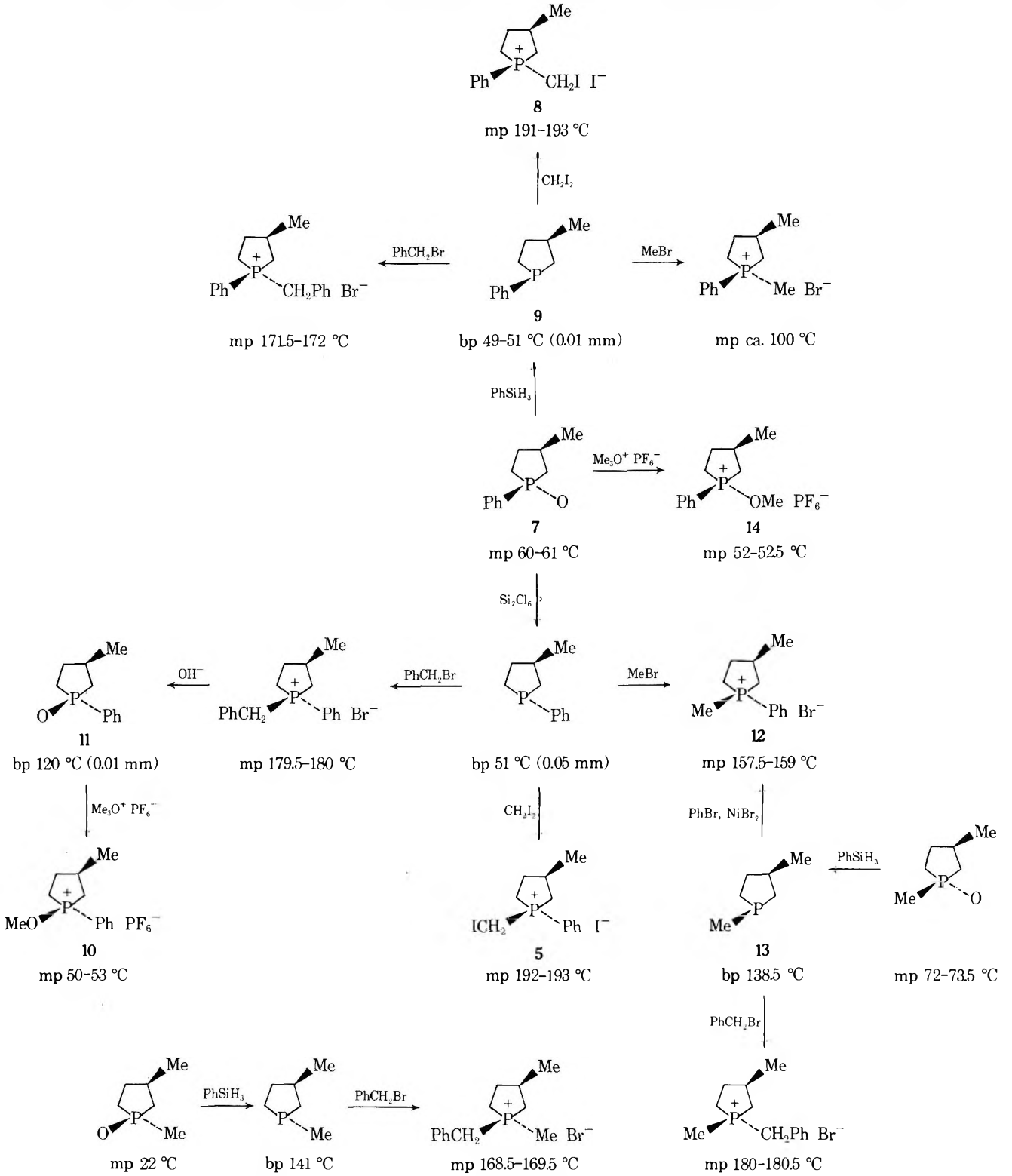
catalytic hydrogenation of 1,3-dimethyl-3-phospholene 1-oxide yields a mixture of the trans and cis isomers of the corresponding phospholane 1-oxide.[5d] Secondly, although it has been shown that acyclic tertiary phosphines may be arylated with bromobenzene in the presence of $NiBr_2$ with retention of configuration at phosphorus,[7a] the stereochemistry of this reaction with cyclic tertiary phosphines has not been tested. Chart I indicates that this arylation has now been demonstrated to occur with predominant if not complete retention of configuration at phosphorus.

Experimental Section

Preparation of *cis*-1-Iodomethyl-3-methyl-1-phenylphospholanium Iodide (5). To 13.6 g (0.070 mol) of *trans*-3-methyl-1-

phenylphospholane 1-oxide (7) in 300 ml of dry benzene under nitrogen was added slowly 24.5 g (0.0911 mol) of hexachlorodisilane. The reaction mixture was quenched by dropwise addition of 60 ml of 30% sodium hydroxide at 0 °C and the benzene layer separated

Chart I. Stereochemical Relationships of Phospholanes Using Reactions of Known Stereochemistry[a,b]



[a] Preparations of these compounds are given in ref 5 except for the methoxyphosphonium salts, *trans*-1,3-dimethyl-1-phenylphospholanium bromide (12), and the iodomethyl salts, which are found in the Experimental Section. Although one enantiomer is shown for each reaction, the reactions and physical properties are for *racemic mixtures* of pure geometrical isomers. [b] Stereochemistry of reactions shown in this chart: quaternization of phosphines with alkyl halides occurs with retention of configuration at phosphorus [L. D. Quin and T. P. Barket, *J. Am. Chem. Soc.*, 92, 4303 (1970); L. Horner, *Pure Appl. Chem.*, 9, 225 (1964)]; phenylsilane reduction of phosphine oxides also occurs with retention of configuration at phosphorus [K. L. Marsi, *J. Org. Chem.*, 39, 265 (1974)]; methylation of phosphine oxides takes place with retention of configuration since no bonds are cleaved at phosphorus; hexachlorodisilane reduction of phospholane oxides is accompanied by predominant inversion of configuration at phosphorus;[5c] hydroxide cleavage of *trans*- and *cis*-1-benzyl-3-methyl-1-phenylphospholanium bromide occurs with retention of configuration at phosphorus[5d] as does the hydroxide cleavage of *trans*- and *cis*-1-benzyl-1,3-dimethylphospholanium bromide.[5a,b]

and dried. Methylene iodide (30.0 g, 0.133 mol) was added with stirring to the benzene layer, the mixture refluxed gently for 1 h, and 17.6 g of crude **5** obtained after filtration. Seven recrystallizations from water gave a material of mp 192–193 °C dec.

Anal. Calcd for $C_{12}H_{17}I_2P$: C, 32.31; H, 3.84. Found: C, 32.04; H, 3.94.

Preparation of *trans*-1-Iodomethyl-3-methyl-1-phenylphospholanium Iodide (8). To 5.0 g (0.0258 mol) of **7** under nitrogen was added 2.8 g of phenylsilane via pipet. The mixture was warmed to about 60 °C. After effervescence ceased (about 0.5 h) the reaction mixture was distilled to give *cis*-3-methyl-1-phenylphospholane (**9**), bp 130–136 °C (5 mm). The distillate was quaternized by adding 6.85 g (0.0257 mol) of methylene iodide in 15 ml of benzene with stirring. The mixture was stored overnight and yielded 5.8 g (0.0130 mol) of **8** upon filtration. One recrystallization from ethanol–ethyl acetate gave **8** of mp 191–193 °C dec. A mixture melting point with **5** gave 177–178 °C.

Anal. Calcd for $C_{12}H_{17}I_2P$; C, 32.31; H, 3.84. Found: C, 32.39; H. 3.91.

Preparation of the Trans and Cis Isomers of 1-Methoxy-3-methyl-1-phenylphospholanium Hexafluorophosphate. For the preparation of the trans isomer (**14**) 2.98 g (0.0153 mol) of the phosphine oxide **7** was dissolved in 25 ml of dry methylene chloride. This solution was added to a suspension of 3.51 g (0.0170 mol) of trimethyloxonium hexafluorophosphate in 50 ml of dry methylene chloride and the resulting mixture stirred at room temperature overnight. Traces of insoluble residue were removed by centrifugation and the supernatant solution evaporated to dryness in vacuo. The glassy residue crystallized upon standing and the resulting crystals were extracted with 150 ml of ether in 10-ml portions. The crystals were then dissolved in methylene chloride and ether added until an oil separated. The oil was washed twice with ether, and upon drying in vacuo it crystallized to yield 1.60 g (0.00452 mol) of **14**, mp 50–52.5 °C.

Anal. Calcd for $C_{12}H_{18}OP_2F_6$: C, 40.69; H, 5.12. Found: C, 40.95; H, 5.40.

The cis isomer (**10**) was similarly prepared from **11**,[5d] mp 50–53 °C; a mixture melting point with **14** gave 29–44 °C.

Anal. Calcd for $C_{12}H_{18}OP_2F_6$: C, 40.69; H, 5.12. Found: C, 40.80; H, 5.39.

Preparation of *trans*-1,3-Dimethyl-1-phenylphospholanium Bromide (12). This compound was prepared from *cis*-1,3-dimethylphospholane (**13**)[5a,b] by the method of Horner,[7a] mp 157.5–159 °C (lit.[5d] 158.5–159 °C).

X-Ray Crystallographic Data. A colorless, transparent parallelepiped of dimensions 0.486 × 0.076 × 0.064 mm^3 was used for the x-ray analysis. Since the material appeared hygroscopic, a crystal was mounted on a glass fiber and sealed in a Lindemann glass capillary tube for collection of the x-ray data. Preliminary Weissenberg and precession photographs showed the following conditions for reflection: *hkl*, no conditions; 0*k*0, $k = 2n$; *h*0*l*, $l = 2n$, uniquely determining space group at $P2_1/c$. A pseudo-A-centering condition was also exhibited which helped in interpretation of the Patterson map.

Precise unit cell parameters were obtained by a least-squares refinement of 18 independent 2θ values obtained from a manual G.E. XRD-5 diffractometer equipped with a scintillation counter as a detector and using Mo Kα radiation. (Crystal data are given in Table I.)

Table I. Crystal Data

Mol wt 446.051	$F(000) = 840$
Monoclinic, space group $P2_1/c$	
$a = 7.217$ (3) Å	
$b = 14.261$ (6) Å	$\beta = 106.54°$ (3)
$c = 14.778$ (6) Å	
Volume of the unit cell = 1458 Å^3	$D_{calcd} = 2.03$ g/cm^3
Molecules/unit cell = 4	$D_{exp} = 2.12$ g/cm^3

Linear absorption coefficient, μ(Mo K$_\alpha$) = 44.473 cm^{-1}
Crystal dimensions: 0.486 × 0.076 × 0.064 mm
Crystal was bound by faces {100}, {0$\bar{1}$1}, and {011}, respectively.

Data were collected out to a 2θ of 45° using 60-s scans at a scan rate of 2° min^{-1}, counting backgrounds for 10 s on either side of the peak. Three standard reflections were measured every 2 h. A scale factor calculated from these was used to scale each block of data to zero time. The average value of the scale factor over the complete data collection was 1.006 with a standard deviation of 0.026, indicating no significant deterioration of the crystal or variation of conditions. The crystal did change to a yellowish-brown color during the course of the data collection. A total of 1946 reflections was measured with 1434 considered observed based on the criteria $I > 3\sigma(I)$. Unobserved data were given zero weight and not included in the refinement.

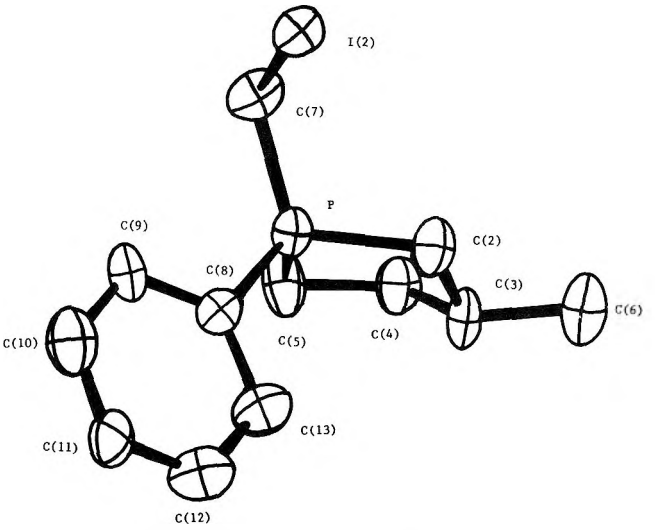


Figure 1. ORTEP drawing of the molecule. Thermal ellipsoids have been scaled to include 50% probability.

Backgrounds were corrected for counting times and Lorentz and polarization factors were applied in the normal manner.[8] Initially the data were not corrected for absorption, but a final correction using Tompa's method[9] gave maximum and minimum transmission coefficients of 0.77 and 0.72, respectively. Weights were calculated according to the method proposed by Stout and Jensen,[10] $\sigma(F) = \{(k/4LpI)[\sigma^2(I) + (0.05I)^2]\}^{1/2}$. Scattering factors for the iodide ion were taken from Cromer and Mann.[11] Scattering factors for all other nonhydrogen atoms were from the International Tables[12] with hydrogen scattering factors taken from the calculations of Stewart, Davidson, and Simpson.[13] Anomalous scattering corrections were assumed to be the same for both the iodine atom and iodide ion and were from the International Tables for Crystallography.[12] No correction was made for extinction but 39 reflections were finally removed from the data because of obvious error in crystal setting, irregularly shaped backgrounds, short-term variations in instrumental stability, and other errors related to the data collection.

Structure Analysis and Refinement. The structure was solved from the three-dimensional Patterson function by location of the iodine positions. The Fourier synthesis phased on the iodine atom showed the locations of all the other atoms except hydrogen. Refinement of these atomic positions and the anisotropic thermal parameters gave a standard R factor of 0.066. A difference Fourier map failed to indicate well-defined hydrogen atom positions. Examination of the data indicated some obvious errors in data collection indicated above. After removal of the 39 reflections with these obvious experimental errors all hydrogen atoms were evident in the difference Fourier. Four additional cycles of full matrix refinement of positional parameters of all atoms, anisotropic thermal parameters of heavy atoms, and isotropic temperature factors of the hydrogen atoms produced an R factor of 0.045 for the observed data only; the R factor for both the observed and unobserved data was 0.085. The weighted $R(\Sigma w\Delta F^2/\Sigma wF_o^2)^{1/2}$ was 0.059 and S, the standard deviation of an observation of unit weight $[\Sigma w\Delta F^2/(m - n)]^{1/2}$ (m is the number of observations and n is the number of parameters), was 1.87. Final shifts in heavy atom parameters were less than 10% of their standard deviations and the corresponding shifts in the hydrogen parameters were less than 25% of their standard deviations. A final difference map was essentially flat except for areas around the iodine atom and ion, where peak heights varied from +1.30 to −0.51 eA^{-3}. A $\delta(R)$ normal probability plot[14] was calculated and was essentially linear; the equation of the least-squares straight line had a slope of 1.7 and an intercept of −0.04. The slope of this line indicates that the $\sigma(F)$ are underestimated by a factor of about 1.7.

Table II lists final positional and thermal parameters, Figure 1 is an ORTEP drawing of the molecule, and Table III gives the bond distances and angles.

Table II. Positional and Thermal Parameters with Their Standard Deviations in Parentheses

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
I(1)	0.90818 (10)[a]	0.88611 (5)	0.22996 (5)	0.02025 (20)	0.00576 (5)	0.00565 (5)	0.00011 (7)	0.00348 (7)	0.00087 (3)
I(2)	0.30387 (9)	0.61494 (5)	0.24359 (4)	0.01933 (18)	0.00569 (5)	0.00376 (4)	0.00044 (7)	0.00286 (6)	0.00012 (3)
P	0.3556 (3)	0.7580 (2)	0.0815 (2)	0.0127 (5)	0.0034 (1)	0.0042 (1)	0.0004 (2)	0.0022 (2)	0.0000 (1)
C(2)	0.1005 (12)	0.7451 (7)	0.0187 (6)	0.0165 (23)	0.0045 (6)	0.0047 (6)	0.0011 (9)	0.0036 (9)	0.0006 (4)
C(3)	0.0556 (13)	0.8258 (8)	−0.0483 (7)	0.137 (22)	0.0057 (7)	0.0065 (6)	0.0020 (10)	0.0033 (10)	0.0011 (5)
C(4)	0.1750 (15)	0.9089 (7)	−0.0017 (7)	0.0193 (24)	0.0042 (6)	0.0064 (7)	0.0018 (10)	0.0049 (11)	0.0009 (5)
C(5)	0.3791 (13)	0.8767 (6)	0.0427 (7)	0.0155 (23)	0.0034 (5)	0.0057 (6)	0.0000 (8)	0.0029 (9)	−0.0004 (4)
C(6)	−0.1623 (16)	0.8452 (9)	−0.0486 (5)	0.0195 (28)	0.0072 (7)	0.0075 (8)	−0.0005 (12)	−0.0019 (12)	−0.0003 (7)
C(7)	0.3939 (14)	0.7515 (7)	0.2060 (7)	0.0193 (25)	0.0046 (6)	0.0048 (6)	−0.0005 (9)	0.0027 (9)	−0.0016 (5)
C(8)	0.5047 (12)	0.6768 (6)	0.0426 (5)	0.0126 (20)	0.0041 (5)	0.0030 (5)	−0.0014 (8)	0.0025 (8)	0.0003 (4)
C(9)	0.4522 (16)	0.6515 (7)	−0.0516 (7)	0.0275 (29)	0.0038 (6)	0.0048 (6)	0.0010 (11)	0.0040 (11)	0.0004 (5)
C(10)	0.5658 (17)	0.5905 (7)	−0.0825 (6)	0.0348 (35)	0.0056 (7)	0.0027 (5)	0.0022 (12)	0.0063 (11)	−0.0005 (5)
C(11)	0.7267 (14)	0.5531 (7)	−0.0230 (8)	0.0187 (26)	0.0033 (6)	0.0072 (8)	−0.0025 (9)	0.0042 (12)	−0.0017 (5)
C(12)	0.7787 (14)	0.5771 (7)	0.0651 (8)	0.0148 (23)	0.0048 (6)	0.0068 (7)	−0.0001 (10)	−0.0004 (10)	−0.0002 (6)
C(13)	0.6677 (13)	0.6387 (6)	0.1052 (7)	0.0147 (23)	0.0047 (6)	0.0050 (6)	−0.0006 (9)	0.0023 (9)	−0.0001 (5)
H2(1)	0.057 (16)	0.670 (9)	−0.013 (7)	8. (3)[b]					
H2(2)	0.017 (13)	0.736 (6)	0.55 (6)	5. (2)					
H3(3)	0.097 (11)	0.843 (6)	−0.091 (5)	3. (2)					
H4(4)	0.119 (11)	0.929 (6)	0.037 (6)	4. (2)					
H4(5)	0.171 (14)	0.970 (7)	−0.051 (7)	6. (3)					
H5(6)	0.440 (13)	0.875 (6)	−0.002 (6)	4. (2)					
H5(7)	0.449 (8)	0.907 (4)	0.094 (4)	0. (1)					
H6(8)	−0.234 (14)	0.791 (7)	−0.112 (7)	6. (3)					
H6(9)	−0.233 (18)	0.868 (7)	−0.032 (8)	7. (3)					
H6(10)	−0.213 (15)	0.893 (7)	−0.129 (7)	8. (3)					
H7(11)	0.510 (15)	0.758 (6)	0.234 (6)	5. (2)					
H7(12)	0.310 (8)	0.805 (4)	0.222 (4)	0. (1)					
H9(13)	0.351 (11)	0.678 (6)	−0.093 (5)	4. (2)					
H10(14)	0.536 (8)	0.576 (4)	−0.144 (4)	0. (1)					
H11(15)	0.774 (12)	0.502 (6)	−0.045 (6)	5. (2)					
H12(16)	0.874 (10)	0.550 (5)	0.114 (5)	3. (2)					
H13(17)	0.714 (9)	0.662 (4)	0.178 (4)	1. (1)					

[a] The form of the anisotropic temperature factor expression is exp $(\Sigma_{i=1}^{3} \Sigma_{j=1}^{3} h_i h_j \beta_{ij})$. [b] Isotropic temperature factors are given for hydrogen atoms.

Table III. Bond Distances and Angles with Their Standard Deviations in Parentheses

A. Bond Distances

P(1)–C(2)	1.82 (1)	C(2)–H(21)	1.2 (1)
C(2)–C(3)	1.49 (1)	C(2)–H(22)	0.9 (1)
C(3)–C(4)	1.51 (1)	C(3)–H(31)	0.8 (1)
C(4)–C(5)	1.50 (1)	C(4)–H(41)	0.8 (1)
P(1)–C(5)	1.81 (1)	C(4)–H(42)	1.1 (1)
P(1)–C(7)	1.78 (1)	C(5)–H(51)	0.9
C(3)–C(6)	1.54 (1)	C(5)–H(52)	0.90
P(1)–C(8)	1.78 (1)	C(6)–H(61)	1.0
P(1)–C(7)	1.78 (1)	C(6)–H(62)	1.3
C(7)–I(2)	2.17 (1)	C(6)–H(63)	0.9 (1)
C(8)–C(9)	1.38 (1)	C(7)–H(72)	1.04
C(9)–C(10)	1.36 (2)	C(7)–H(71)	0.8
C(10)–C(11)	1.35 (2)	C(9)–H(91)	0.9
C(11)–C(12)	1.35 (2)	C(10)–H(101)	0.9
C(12)–C(13)	1.39 (1)	C(11)–H(111)	0.9
C(13)–C(8)	1.38 (1)	C(12)–H(121)	0.9
		C(13)–H(131)	1.08

B. Bond Angles

C(2)–P–C(5)	96.0 (4)	C(3)–C(6)–H(8)	112 (6)
C(2)–P–C(8)	112.7 (4)	C(3)–C(6)–H(9)	111 (5)
C(2)–P–C(7)	111.0 (4)	H(10)–C(6)–H(9)	102 (8)
C(5)–P–C(7)	112.0 (5)	H(10)–C(6)–H(8)	104 (9)
C(5)–P–C(8)	112.7 (4)	H(9)–C(6)–H(8)	104 (8)
P–C(5)–C(4)	104.8 (7)	C(3)–C(2)–H(2)	116 (6)
C(5)–O(4)–C(3)	108.7 (8)	C(3)–C(2)–H(1)	117 (6)
C(4)–C(3)–O(2)	108.3 (8)	H(2)–C(2)–H(1)	87 (8)

B. Bond Angles

C(3)–O(2)–P	104.9 (7)	P–C(2)–H(1)	114 (6)
C(4)–C(3)–C(6)	114.3 (9)	C(8)–C(9)–H(13)	121 (5)
P–C(8)–C(9)	118.5 (7)	H(13)–C(9)–C(13)	120 (5)
P–C(8)–C(13)	121.0 (7)	C(9)–C(10)–H(14)	120 (4)
C(8)–C(9)–C(10)	119.1 (9)	H(14)–C(10)–C(11)	119 (4)
C(9)–C(10)–C(11)	122 (1)	C(10)–C(11)–H(15)	115 (6)
C(10)–C(11)–C(12)	120 (1)	H(15)–C(11)–C(12)	123 (6)
C(11)–C(12)–C(13)	121 (1)	C(11)–C(12)–H(16)	124 (5)
C(12)–C(13)–C(8)	117.6 (9)	H(16)–C(12)–C(13)	114 (5)
P–C(5)–H(7)	105 (4)	C(12)–C(13)–H(17)	122 (3)
H(7)–C(5)–H(6)	112 (7)	C(8)–C(13)–H(17)	121 (3)
C(4)–C(5)–H(6)	108 (6)		
C(5)–C(4)–H(5)	111 (5)		
H(5)–C(4)–H(4)	105 (8)		
C(3)–C(4)–H(4)	105 (6)		
C(4)–C(3)–H(3)	80 (5)		
H(3)–C(3)–C(6)	104 (6)		
C(3)–C(6)–H(10)	122 (7)		

Discussion

The methyl group is trans to the phenyl group and is in an equatorial position, thus establishing the stereochemical configuration. The phospholanium ring system appears to be in the envelope form with the methyl group equatorial at the point of flap [C(3)] (Figure 1). A comparison of the phospholanium ring system with the half-chair form and the envelope form of cyclopentane is given in Figure 3.[17] The longer P–C bonds, compared to normal C–C bonds, cause considerable variations in the bond angles when compared to cyclopentane.

The equations for the various planes are given in Table

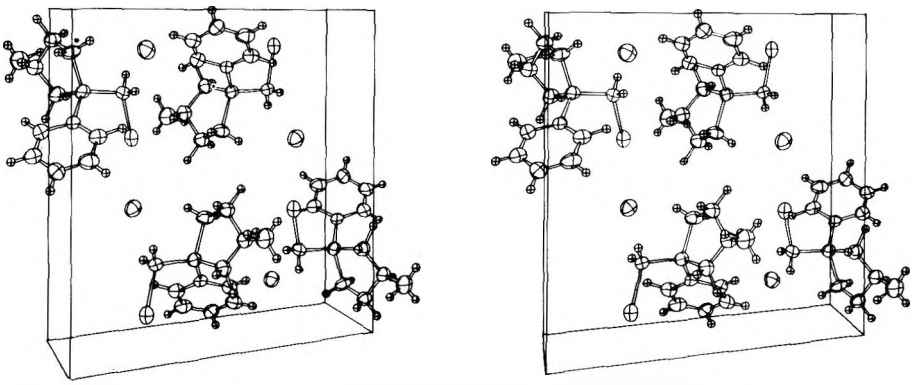
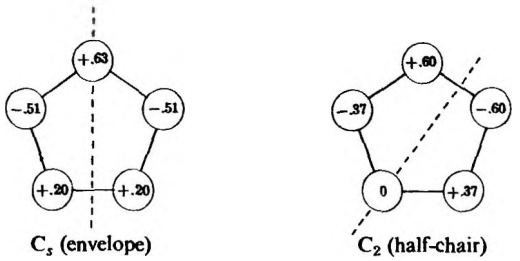


Figure 2. ORTEP drawing illustrating the packing of the molecules in the unit cell. Thermal ellipsoids have been scaled to include 50% probability; hydrogen atoms have been assigned an isotropic temperature factor of 1.0 for the sake of clarity.



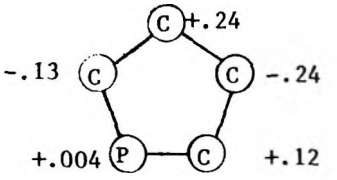


Figure 3. Comparison of the envelope and half-chair forms of cyclopentane[17] and the phospholanium ring system. Figures indicate displacement of atoms in angstroms, above (positive) or below (negative) the plane of the paper.

Table IV

Atoms in Plane	*l*	*m*	*n*	$p^{a,b}$	$S(\Delta^2)^c$
C(8), C(9), C(10) C(11), C(12), C(13)	0.618	0.763	−0.189	9.38	0.0002
P, C(2), C(4), C(5)	−0.438	0.272	0.857	2.89	0.019
C(2), C(3), C(4)	−0.880	0.282	0.382	2.53	
C(8), P, C(2)	0.310	0.659	−0.686	7.02	
P, C(2), C(3) C(4), C(5)	−0.559	0.290	0.776	2.80	0.151

[a] Least-squares plane; $lX + mY + nZ - p = 0.0$. [b] Coordinate system for plane is X along a, Y in a–b plane, z along c. [c] $S(\Delta^2)$ is the sum of the squares of the deviations of atoms from the planes.

IV. The angle formed between the plane of the phenyl group and the C(8)–P–C(2) plane is 34°. The plane of the phenyl group makes an angle of 77° with the C(5)–C(4)–P–C(2) plane. The plane of C(2)–C(3)–C(4) forms an angle of 38° with P–C(5)–C(4)–C(2).

Comparison of this structure to the structure of methylphenylphospholanium iodide[3] shows that all angles and distances are within three standard deviations of one another. The sum of the angles in the phospholanium ring of methylphenylphospholanium iodide is 516° while the sum of the internal angles in the phospholanium ring in this structure is 523°.

A packing diagram is shown in Figure 2. An iodide–iodine distance of 3.672 (1) Å is observed in this structure, which is significantly less than the sum of the van der Waals radii of 4.3 Å.[15] An intermolecular distance of 3.76 Å between two iodine atoms has been observed in hexaiodobenzene.[16] The polarizable nature of the iodine atom probably accounts for the unusually close approaches observed in these structures. There appear to be no other intermolecular interactions that are significantly less than the sum of the van der Waals radii.

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Registry No.—**5**, 57664-91-2; **7**, 57664-92-3; **8**, 57664-93-4; **9**, 57664-94-5; **10**, 55043-89-5; **12**, 57664-95-6; **14**, 55043-91-9.

References and Notes

(1) The cis and trans designations are in accordance with the *Chemical Abstracts* system by which, for example, the cis isomer has the senior groups (as defined by the sequence rule) on the same side of reference plane of the ring; cf. *Chem. Abstr.*, **76**, 851 (1972), and also *J. Chem. Inform. Computer Sci.*, **15**, 67 (1975).
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(8) Computer programs used were by F. R. Ahmed and co-workers (NRC-2, Data Reduction; NRC-8, Fourier for Distorted and Undistorted Nets; and NRC-12, Scan of Interatomic Distances and Angles, National Research Council, Ottawa, Ontario, Canada), Busing and Levy (ORFLS), and Carrol K. Johnson (ORTEP). These programs were locally modified for use with the XDS Sigma 7 computer. Other programs were written locally by G. D. Smith, E. L. Enwall, and C. N. Caughlan.
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Synthesis of Monoesters of Aryl- (or alkyl-) phosphonic Acids of Selected Arenols. A Study of the Effect of Dimethylformamide on the Preparation of 2-Naphthylphenylphosphonic Acid via Proton and Phosphorus-31 Nuclear Magnetic Resonance Analysis[1]

William Ronald Purdum[2a] and Kenneth Darrell Berlin*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

Susan J. Kelly[2b] and Larry G. Butler*

Department of Biochemistry, Purdue University, West Lafayette, Indiana 47907

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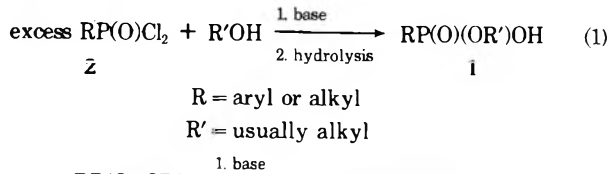
The general synthesis of aryl- (or alkyl-) phosphonate monoesters of selected arenols has been accomplished in good yield by reaction of the substituted phosphonic dichloride with the arenol in pyridine solvent. Careful hydrolysis of the reaction mixture gave the phosphonate monoester which was isolated as the ammonium salt from acetone–ether (1:2). A comprehensive study of the preparation of 2-naphthyl phenylphosphonate revealed that the yield was enhanced by premixing of the phosphonic dichloride with dimethylformamide in pyridine prior to the addition of the arenol in pyridine. The influence of dimethylformamide on the reaction path has been studied by ^{1}H NMR and ^{31}P NMR analysis.

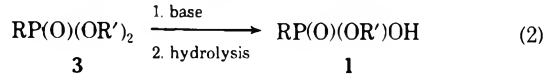
It has recently been shown that monoesters of phosphonic acids **1** are good substrates for certain phosphodiesterase enzymes which are widely distributed in nature.[3] Phosphonate monoesters have several advantages over conventional substrates, usually complex nucleotide phosphodiesters, or the simple diester, bis(4-nitrophenyl)phosphate, for assaying these enzymes.[4] For example, phosphonate monoesters readily and conveniently distinguish[4] between 5′-nucleotide phosphodiesterases and other phosphodiesterases.[5] In light of the elevated levels of 5′-nucleotide phosphodiesterase activity in fast-growing rat hepatomas[6] and the suggested diagnostic value of 5′-nucleotide phosphodiesterase isoenzyme patterns in the sera of human hepatic cancer patients,[7,8] considerable interest in phosphonate monoesters as enzyme substrates for diagnostic and analytical purposes can be expected. We have thus investigated the preparation of these compounds.

The preparation of phosphonate monoesters **1** has normally been accomplished via (a) reaction of an excess of an appropriate phosphonic dichloride **2** with an aliphatic alcohol (thus minimizing diester formation)[9] and subsequent hydrolysis to the phosphonate monoester or (b) by the synthesis of the aliphatic phosphonate diester **3** by known methods[10] followed by a controlled basic hydrolysis to the monoacid ester **1** (2).[11] These procedures, although affording good yields, have been primarily limited to the preparation of monoacid esters derived from aliphatic alcohols and not arenols.



(1)

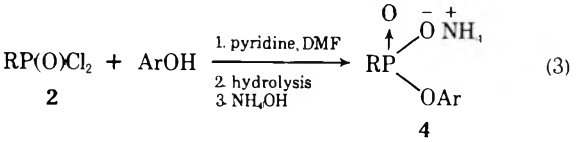
R = aryl or alkyl
R′ = usually alkyl



(2)

R = aryl, alkyl
R′ = alkyl

The scarcity of good methods for phosphonate monoesters of arenols is likely the result of the known low reactivity of the oxygen atom of the arenol with respect to a weak electrophilic center such as the phosphorus atom of a phosphonic dichloride. However, we have synthesized several phosphonate monoesters in good yield (isolated as the ammonium salts **4**), via the reaction in pyridine solvent of a selected phosphonic dichloride with a suitable arenol. The results of 11 such syntheses are listed in Table I. An observation that dimethylformamide (DMF) greatly influenced the reaction prompted us to make a careful study of the process with one case. As can be noted from Table II, the influence of dimethylformamide on the yield of the overall reaction (eq 3) (R = C_6H_5; Ar = 2-$HOC_{10}H_7$) is dramatic. Without DMF, the variation in the yield of monoester is considerable and, as expected, is very dependent upon the concentration of both the phosphonic dichloride and the arenol. Owing to the expense and difficulty in obtaining



(3)

R = C_6H_5, C_6H_{11}, C_3H_7, CH_3, $ClCH_2$
Ar = 2-$HOC_{10}H_7$, 4-$O_2NC_6H_4$

most of the initial phosphonic dichlorides, maintenance of their concentrations at a minimum level during the synthesis is economically desirable. For example, the yield of isolated monoester **4** (R = C_6H_5; Ar = 2-$C_{10}H_7$) decreases with decreasing concentration of phenylphosphonic dichloride and increasing concentration of 2-naphthol. This result is

Table I. Summary of Synthesis of Phosphonate Monoesters $RP(O)(OAr)ONH_4$

R	Ar	Molecular formula	Separation technique[a]	Yield, %[b]	R_f[e]	Ir,[f] ν cm^{-1} P → O	Anal. % Found (calcd) C	H	P
C_6H_5	p-$O_2NC_6H_4$	$C_{12}H_{13}N_2O_5P$	C_6H_6	20,[c,d] 58	0.73	1185 (1053)	48.78 (48.64)	4.70 (4.42)	10.69 (10.57)
C_6H_5	2-$C_{10}H_7$	$C_{16}H_{16}NO_3P\cdot\frac{1}{2}H_2O$	C_6H_6	72,[c] 78	0.75	1215 (1057)	62.46 (61.93)	5.63 (5.48)	10.49 (10.29)
c-C_6H_{11}	p-$O_2NC_6H_4$	$C_{12}H_{19}N_2O_5P$	C_6H_6	53	0.80	1190 (1060)	47.95 (47.68)	6.40 (6.29)	10.00 (10.26)
n-C_3H_7	p-$O_2NC_6H_4$	$C_9H_{15}N_2O_5P$	$HCCl_3$	53	0.74	1171 (1054)	41.23 (41.22)	5.90 (5.73)	12.09 (11.83)
n-C_3H_7	2-$C_{10}H_7$	$C_{13}H_{18}NO_3P$	C_6H_6	59	0.75	1165 (1055)	58.16 (58.43)	6.99 (6.74)	11.30 (11.61)
2-C_3H_7	p-$O_2NC_6H_4$	$C_9H_{15}N_2O_5P\cdot\frac{1}{2}H_2O$	$HCCl_3$	51	0.75	1175 (1060)	39.33 (39.85)	6.14 (5.90)	11.41 (11.83)
2-C_3H_7	2-$C_{10}H_7$	$C_{13}H_{18}NO_3P$	C_6H_6	60	0.76	1154 (1058)	58.33 (58.43)	6.66 (6.74)	11.21 (11.61)
$ClCH_2$	p-$O_2NC_6H_4$	$C_7H_{10}ClN_2O_5P$	$HCCl_3$	40	0.62	1213 (1065)	31.05 (31.28)	3.84 (3.72)	11.31 (11.54)
$ClCH_2$	2-$C_{10}H_7$	$C_{11}H_{13}ClNO_3P$	C_6H_6	44	0.68	1200 (1064)	48.41 (48.26)	4.85 (4.75)	11.30 (11.33)
CH_3	p-$O_2NC_6H_4$	$C_7H_{11}N_2O_5P$	$HCCl_3$	43	0.59	1220 (1067)	35.94 (35.90)	4.95 (4.70)	13.21 (13.25)
CH_3	2-$C_{10}H_7$	$C_{11}H_{14}NO_3P$	C_6H_6	64	0.63	1160 (1061)	51.06 (51.36)	6.12 (6.30)	11.82 (12.10)

[a] C_6H_6 refers to benzene extraction and $HCCl_3$ to chloroform extraction of water layer. [b] Percentage calculated on basis of limiting component. All compounds were chromatographically pure. The ratio of arenol:dichloride was 1:1 with the one exception in *c* below; solvent was pyridine (no DMF present). [c] Ratio of arenol:dichloride was 1:3 but acid not added to maximize extraction into benzene. Ester isolated in acid rather than in salt form by recrystallization from boiling water after removal of benzene in vacuo.[4] [d] An analysis was also performed on the free acid obtained as described in footnote *c*. Anal. Calcd for $C_{12}H_{10}NO_5P$: C, 51.62; H, 3.61; N, 5.01; P, 11.09; mol wt, 279.1. Found: C, 51.42; H, 3.62; N, 4.91; P, 11.00; mol wt, 280. [e] On ascending paper chromatography using 2-propanol–H_2O–NH_4OH (80:20:0.2). [f] The ir spectra show the top band for the asymmetric stretch while the lower band is the symmetric stretch; for a review of the ir frequencies of a few members of this family, see L. G. Thomas, "Interpretation of the Infrared Spectra of Organophosphorus Compounds", Heyden, London, 1974, Chapter 15.

expected if the amount of diester formed correspondingly increases. However, attempts to isolate appreciable amounts of diester from this reaction solution even with large excesses of 2-naphthol have been difficult (the presence of diester **5** in the reaction mixture in good yield was confirmed spectrally) because of the general work-up procedure to obtain **4**; solubility properties of 2-naphthol and the diester **5** are very similar. The important observation to be made in viewing the data of Table II is that the addition of 1 equiv of DMF [with respect to $C_6H_5P(O)Cl_2$] to the reaction mixture afforded a twofold increase in the amount of phosphonate monoester, **4** (R = C_6H_5; Ar = 2-$C_{10}H_7$) formed even with a *large excess* of the arenol. It is worthy of mention that excess 2-naphthol was easier to remove in the work-up than $C_6H_5P(O)(OH)_2$ which formed when excess $C_6H_5P(O)Cl_2$ was present prior to hydrolysis.

In all cases utilizing DMF, the phenylphosphonic dichloride and DMF are premixed in pyridine before being added to 2-naphthol in pyridine. This premixing is an important consideration when it is noted that the combination of phenylphosphonic dichloride–DMF is very similar to a typical Vilsmeier reagent: DMF–phosphorus oxychloride. Thus, premixing could lead to formation of a complex with a different reactivity (with respect to 2-naphthol) than the noncomplexed phosphonic dichloride. In order to test this hypothesis and to gain some insight regarding the intermediates present, the course of the reaction of phenylphosphonic dichloride with 2-naphthol was followed via ^{31}P nuclear magnetic resonance, with and without added DMF; see Table III.

Before the addition of DMF or 2-naphthol, the ^{31}P resonance of phenylphosphonic dichloride **2** (R = C_6H_5) in pyridine was observed at −34.3 ppm[12] (relative to H_3PO_4) along with a very minor second resonance at −18.8 ppm

Table II. Effect of Concentration of Phenylphosphonic Dichloride, 2-Naphthol, and Added Dimethylformamide on the Yield of 2-Naphthyl Phenylphosphonate[a]

$C_6H_5P(O)Cl_2$ rel concn	2-$HOC_{10}H_7$ rel concn	DMF rel concn	Yield of monoester,[b] %
3	1		94.9
2	1		82.3
1	1		78.6
1	2		49.9
1	3		42.6
1	3	1	80.5
1	3	2	85.6

[a] Taken in part from the Ph.D. Thesis of S. J. Kelly, Purdue University, 1974. [b] Yields are uncorrected for any water of hydration and are for the ammonium salt of the monoester, calculated on basis of the limiting reactant, $C_6H_5P(O)Cl_2$ or 2-$C_{10}H_7OH$.

(sample A). This high-field ^{31}P resonance was observed in all of the initial spectra and may be tentatively attributed to slow complexation of pyridine with **2** (R = C_6H_5). The concentration of this "complex" slowly increased with time. Although the presence of phenylphosphonic acid is unfavorable under our anhydrous conditions, its ^{31}P resonance has been observed, for example, at −17.5 ppm in acetone.[13] However, in the present study the ^{31}P resonance of phenylphosphonic acid (as the dipyridinium salt) was observed only at −10.2 ppm in pyridine in very good agreement with the reported values of −10.8 ($2NH_4^+$ salt)[14a] and −10.9 ppm [$2(CH_3)_4N^+$ salt][14b] for other ammonium salts. The presence of phenylphosphonic acid can also be eliminated from consideration since the resonance of −18.7 ppm was observed to disappear slowly upon the addition of 2-naphthol or DMF. Phenylphosphonic acid would not be expect-

Table III. ^{31}P Resonances Observed in the Reaction of Phenylphosphonic Dichloride with 2-Naphthol in Pyridine[a]

Sample[b]	Time[c]	^{31}P resonance position, ppm	Rel abundance, %
A		−34.3	97.8
		−18.8	2.2
B	t_0 + 10 min	−12.1	57.1
		−9.5	29.6
		−6.1	13.3
B	t_0 + 12 h	−12.1	64.9
		−9.5	35.1
C	t_0	−34.3	7.6
		−18.7	13.2
		−1.5	62.0
		+0.12	17.2
C	t_0 + 10 min	−1.5	66.4
		+1.0	33.6
D	t_0 + 10 min	−12.0	20.3
		−9.3	72.5
		−6.4	7.2
D	t_0 + 12 h	−12.0	20.2
		−9.2	79.8

[a] The ^{31}P resonances are relative to H_3PO_4 as 0.00 ppm. [b] A, 3 g (0.015 mol) of $C_6H_5P(O)Cl_2$ dissolved in 5 ml of pyridine; B, a 5-ml aliquot of 3.9 g (0.02 mol) of $C_6H_5P(O)Cl_2$ + 11.5 g (0.08 mol) of 2-$C_{10}H_7OH$ in 35 ml of pyridine; C, 3 g (0.015 mol) of $C_6H_5P(O)Cl_2$ and 1.1 g (0.015 mol) of DMF in 5 ml of pyridine; D, a 5-ml aliquot of 3.9 g (0.02 mol) of $C_6H_5P(O)Cl_2$ + 1.5 g (0.02 mol) of DMF + 11.5 g (0.08 mol) of 2-$C_{10}H_7OH$ in 35 ml of pyridine. [c] The time t_0 in all cases is within 3 min of the time of mixing.

ed to react with either of these reagents under the conditions of the overall synthesis.

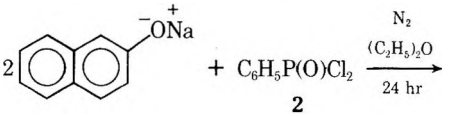
The addition of phenylphosphonic dichloride in pyridine to 4 equiv of 2-naphthol also in pyridine caused a complete disappearance of resonances at −34.3 and −18.8 ppm with appearance of three new resonances at −12.1, −9.5, and −6.1 ppm (sample B) within 10 min of mixing. After 12 min at room temperature, only the ^{31}P resonances at −12.1 (64.9%) and −9.5 (35.1%) ppm were observed, and the relative abundance of these two resonances did not fluctuate appreciably with extended times. The addition of 1 equiv of DMF to **2** (R = C_6H_5) in pyridine (no 2-naphthol present) immediately afforded the appearance of four ^{31}P resonances (C, Table III). After 10 min, the two ^{31}P resonances (−34.3 and −18.7 ppm) attributable to **2** (R = C_6H_5) dissolved in pyridine disappeared. The two remaining resonances (−1.5 and +1.10 ppm), thus, could be due to complexation of DMF with **2** (R = C_6H_5). However, the addition of a solution of **2** (R = C_6H_5) and DMF in pyridine to 4 equiv of 2-naphthol also in pyridine (D, Table III) afforded only the same three ^{31}P resonances (−12.0, −9.3, and −6.4 ppm) observed without the presence of DMF (B, Table III). After 12 h, again only two resonances [−12.0 (20.2%) and −9.2 ppm (79.8%)] remained. Therefore, with or without DMF, intermediates similar in configuration (electronic and steric) about phosphorus are apparently present prior to hydrolysis. However, the relative abundance of these intermediates is drastically different (from Table III): (a) −12.1 (64.9%, B, no DMF) and −12.0 ppm (20.2%, D, DMF); (b) −9.5 (35.1%, B, no DMF) and −9.2 ppm (79.8%, D, DMF). Thus, the presence of DMF increased the concentration of an intermediate (that which had a signal at −9.2 ppm) which apparently led to monoester formation upon hydrolysis (based on the results obtained in Table II with and without DMF and with an excess of 2-naphthol).

Since the presence or absence of the diester di-2-naphthyl phenylphosphonate (**5**) must also be determined in these reaction mixtures, it was necessary to synthesize an authentic sample. Diester **5** was obtained by a modification of a synthetic procedure normally used for dialkyl phosphonates (eq 4).[11a] The sodium salt of 2-naphthol was

Table IV. ^{31}P Resonances as a Function of Presence of Dimethylformamide and Pyridine[a]

Sample[b]	Time, h	Solvent	^{31}P resonance position, ppm	Rel abundance, %
$C_6H_5P(O)Cl_2$–DMF		$DCCl_3$	−34.3	90.7
			−18.5	9.3
$C_6H_5P(O)Cl_2$–DMF	3	$DCCl_3$	−34.4	50.5
			−18.5	21.8
			−0.8	15.1
			+0.8	12.5
$C_6H_5P(O)Cl_2$–DMF	12	$DCCl_3$	−34.5	48.3
			−18.7	21.4
			−1.0	14.8
			+0.6	15.5
$C_6H_5P(O)Cl_2$–DMF		$DCCl_3$–pyridine	−34.2	51.5
			−18.5	17.3
			−1.0	19.2
			+0.7	12.0
$C_6H_5P(O)Cl_2$–DMF	12	$DCCl_3$–pyridine	−1.1	66.7
			+0.8	33.3

[a] ^{31}P resonances are relative to H_3PO_4 as 0.0 ppm. [b] ^{31}P resonances of only $C_6H_5P(O)Cl_2$ in $DCCl_3$ was −34.3 ppm.



$$(2\text{-}C_{10}H_7O)_2\overset{O}{\overset{\uparrow}{P}}C_6H_5 \quad (4)$$

5

R = C_6H_5

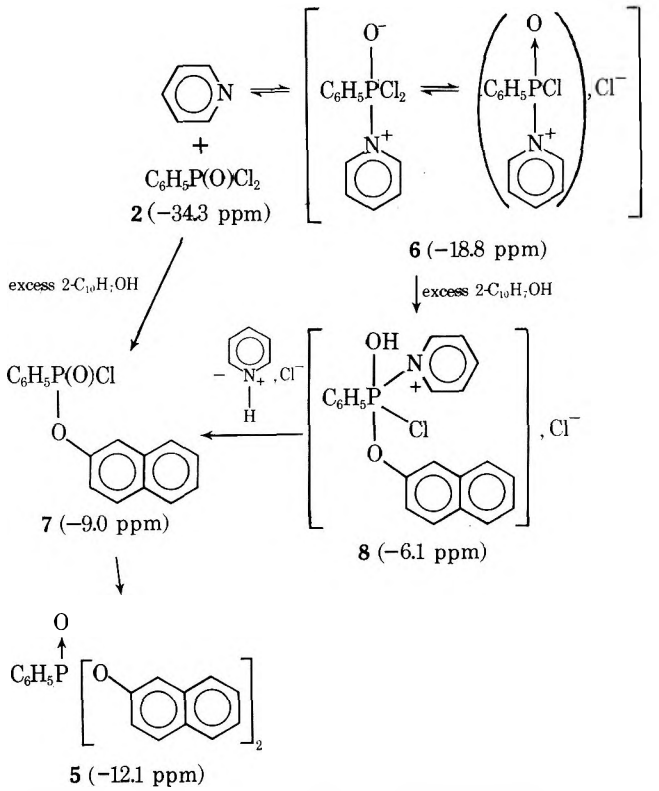
treated with phenylphosphonic dichloride in diethyl ether and upon isolation afforded the diester **5** (30.1%). The ^{31}P resonance of pure diester **5** was determined to be −11.34 ppm in the mixed solvent $DCCl_3$–pyridine. With added DMF before the addition of diester, the ratio of relative abundance of the resonances at −11.7 ppm to that at −9.0 ppm was 0.52. If the diester **5** was present as the low-field resonance (−11.7 ppm), addition of an authentic sample of **5** to this mixture should increase the −11.7-ppm resonance with an overall decrease in the abundance of the −9.0-ppm resonance relative to the −11.7-ppm resonance. The addition of 250 mg of **5** *did increase* the −11.7-ppm resonance, and the ratio of the relative abundance (−11.7 to −9.0 ppm signals) increased slightly to 0.62. Without DMF, the addition of 250 mg of **5** to sample G caused the expected increase in the ratio of relative abundance (−11.4 ppm resonance to the −9.0-ppm resonance) from 1.25 to 1.54. With these observations, the diester **5** was spectrally confirmed to be present in both cases (with and without DMF) and was a major contributor to the low-field resonance. Thus, the signals at −11.34, −11.7, or 12.0 (Table III) are due to **5** predominantly but vary in chemical shift because of shielding changes created by dilution and solute effects.

Before postulating potential reaction paths for phosphonate monoester and diester formation, the dependence of the ^{31}P resonances should be examined as a function of added pyridine or DMF in a noncomplexing solvent ($DCCl_3$ for this system, Table IV). The ^{31}P resonance of −34.3 ppm [phenylphosphonic dichloride (**2**) (R = C_6H_5)] in $DCCl_3$ (without pyridine and DMF) was in agreement with earlier literature reports.[12] The addition of DMF to this solution

caused the immediate appearance of a second ^{31}P resonance at −18.5 ppm (Table IV). After 12 h at room temperature, four resonances were observed (−34.5, −18.7, −1.0, and +0.6 ppm) similar in position to those observed with sample C of Table III. Upon the addition of **2** (R = C_6H_5) and DMF to the mixed solvent system, $DCCl_3$ and pyridine, these four resonances appeared immediately and in approximately the same relative abundance as those which were present without the added pyridine but only after 12 h (Table IV). However, after maintaining the mixture of **2** (R = C_6H_5), DMF, and pyridine in $DCCl_3$ for 12 h at room temperature, only the two high-field resonances (−0.1 and +0.8 ppm) remained. Thus, the presence of pyridine facilitated complexation of **2** (R = C_6H_5) with DMF. The presence of the resonance at −18.5 ppm [previously discussed and assigned solely to the complex of **2** (R = C_6H_5) with pyridine] may also be composed of a signal from the initial adduct of **2** (R = C_6H_5) with DMF and without pyridine. As was observed, the concentration of this adduct would be expected to increase upon mixing and then decrease with extended time as the initial concentration of **2** (R = C_6H_5) decreased.

With the observed positions and relative abundances (as a function of time) for the various ^{31}P resonances of Tables III and IV *without the added DMF*, a tentative path for mono- and diester formation can be formulated (Scheme I). The initial step could involve incomplete formation of adduct **6** from reaction of **2** (R = C_6H_5) and pyridine which provides two observed resonances, −34.3 and −18.8 ppm, respectively. The excess 2-naphthol may then react with noncomplexed **2** (R = C_6H_5) yielding, initially, the monoester acid chloride **7** which is subsequently converted to the diester **5**. If the reaction of 2-naphthol were to occur with the adduct **6**, the new complex **8** formed might be expected to shift to higher field position owing to the changes in electronic charge and configuration about phosphorus.[15]

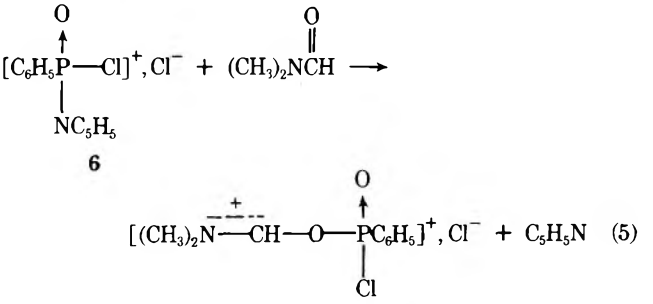
Scheme I[a]



[a] Tentative ^{31}P resonance positions are indicated in parentheses.

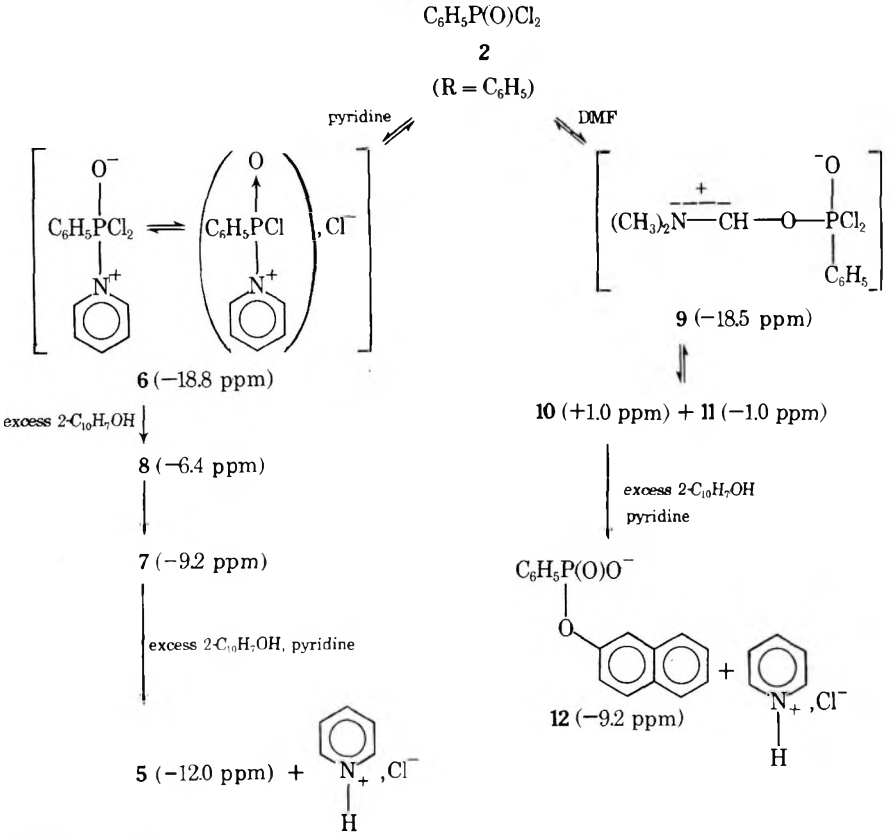
Collapse of this complex **8** could afford more of the monoester acid chloride **7** which could then also form more of the diester **5**. The fact that at least four separate ^{31}P resonances appeared at one time, initially, would indicate that the reaction kinetics are quite complex.

In the presence of 1 equiv of DMF, a slightly different reaction path may be postulated (Scheme II). Complexation of **2** (R = C_6H_5) with pyridine as in Scheme I to again afford **6** is expected owing to the very large excess of pyridine. This intermediate **6** could then react with the excess 2-naphthol to yield **8** which could subsequently be converted to the monoester acid chloride **7** and the diester **5**. However, the increase in the relative abundance for the ^{31}P resonance at −9.3 ppm vs. the diester resonance at low field may be explained by complexation of **2** (R = C_6H_5) with dimethylformamide. This initial complex **9** may fortuitously resonate at the same position as the pyridinium salt **6**. Rapid conversion of **9**, via **10** or **11**, to the monoester acid salt **12** (a new product), which may resonate at the same position as the monoester acid chloride **7**, is not unreasonable. The presence of **12** would hinder further conversion to the diester and thus increase the yield of monoester upon hydrolysis. Without the excess 2-naphthol the conversion of **2** (R = C_6H_5) to **10** and **11** was observed with the appearance of two high-field ^{31}P resonances (~+1 and ~−1.0 ppm assigned to **10** and **11**, respectively). In this regard, the initial pyridine complex **6** in the absence of 2-naphthol may also be converted to the dimethylformamide complex **9** (or **10** or **11**) which might be pictured as a simple displacement of pyridine (eq 5).[16] Of course **10** must be considered a tentative structure. The transformation involving **2** (R = C_6H_5) and DMF into the complexes **9** and **10** (or **11**) is in good agreement with what has been previously reported for the complexes formed between the Vilsmeier reagents, DMF–$POCl_3$.[17]



A ^1H NMR study of the mixture of **2** (R = C_6H_5), DMF, and pyridine in $DCCl_3$ also supported the existence of two structures **10** and **11** but no appreciable amount of **9**. The addition of DMF to **2** (R = C_6H_5) in $DCCl_3$ caused a downfield shift in the resonance of the aldehydic proton (δ 8.01 to 8.11) but only slightly shifted signals for the cis–trans methyl groups of the $(CH_3)_2N$ moiety in **10** (or **11**). Also a very minor difference in separation between the two ^1H resonances [shift 0.3 ppm and $\Delta\delta$ (change in separation between CH_3 resonances) 0.02 ppm] was observed. This system remained constant for at least 72 h at room temperature. However, the addition of pyridine had a dramatic effect. Upon mixing, only a negligible shift in the resonances of the aldehydic protons and the methyl protons was observed. After 12 h, however, two resonances of equal intensity appeared downfield (δ 10.57 and 10.51) for the aldehydic proton plus a broad resonance for the methyl groups of a complex at δ 3.06. These resonances are in addition to those present earlier. Extensive ^{31}P heteroatom decoupling of ^1H of these mixtures indicated that the downfield aldehydic proton resonances were *not* covalently bound

Scheme II[a]



[a] Tentative ^{31}P resonances are indicated in parentheses.

through carbon and oxygen to phosphorus. Thus, ion pairs may be formed which may be the structure of **11**. Such structures have been reported for Vilsmeier complexes formed between DMF and $OPCl_3$.[17]

In summary, a good preparative method has been developed for monophosphonates of the type $RP(O)(OR')ONH_4$. Chemical and NMR evidence is presented which strongly suggest that a Vilsmeier type complex is involved when the arenol and phosphonic dichloride are allowed to react in the presence of pyridine and DMF.

Experimental Section

General Data. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating infrared spectrophotometer as KBr pellets. ^1H NMR and ^{31}P NMR spectra were obtained with a XL-100(15) Varian spectrometer in the solvents indicated (pyridine, $DCCl_3$). Mass spectral analysis was performed on a CEC Model 21 HR unit.

Starting Materials. Phenylphosphonic dichloride was distilled under reduced pressure utilizing the center fraction for all experiments, bp 100–102 °C (4.0 mm). Dimethylformamide was distilled from NaH directly before use. All other phosphonic dichlorides were obtained from Speciality Organics Inc., Irwindale, Calif., and were used without purification. Pyridine was distilled from anhydrous K_2CO_3 also directly before use. Commercially available 2-naphthol was recrystallized (95% C_2H_5OH–H_2O) and dried in vacuo, mp 121–122 °C.

Ammonium 2-Naphthyl Phenylphosphonate (4, R = C_6H_5; Ar = 2-$C_{10}H_7$). A. Without Dimethylformamide. A solution of 7.5 g (0.052 mol) of 2-naphthol in 20 ml of anhydrous pyridine was treated (dropwise) with 1.78 (0.009 mol) of phenylphosphonic dichloride with formation of a light reddish-brown color. This solution was stirred at room temperature for 4 h. Removal of the solvent in vacuo afforded a viscous oil which was dissolved in benzene and extracted with 75 ml of aqueous HCl (8 N). The aqueous layer was then reextracted (2 × 100 ml) with benzene. Evaporation of the organic extracts in vacuo yielded a white semisolid material. This solid was dissolved in acetone (25 ml), the solution of which was warmed and treated dropwise with 1 ml of concentrated NH_4OH (0.015 mol) over a 5-min period and then ether (50 ml) was added. After standing at room temperature for 24 h, the precipitated ammonium salt of 2-naphthylphenylphosphonic acid (**4**) was collected and dried at 35° in vacuo for 24 h: yield 1.3 g (48%); mp 183–185 °C; ir[18] (KBr) ν 3400–2075 (broad, NH_4^+ salt), 1620 and 1600 (aromatic), 1255, 1215, 1139, 1057, 1032, 968, 920, 861, 823, 748, 720, 698, and 644 cm^{-1}; mass spectrum (70 eV) *m/e* 284 ($M^+ - NH_3$); ^1H NMR ($DCCl_3$) δ 7.14–7.98 (m, $C_{10}H_7$ and C_6H_5, 12 H), 8.40–9.40 (broad, NH_4^+).

B. With Dimethylformamide. A solution of 7.5 g (0.052 mol) of 2-naphthol in 20 ml of anhydrous pyridine was treated (dropwise) with a dark red colored mixture of 1.78 g (0.009 mol) of phenylphosphonic dichloride and 0.66 g (0.009 mol) of DMF in 15 ml of pyridine. The resulting dark red solution was stirred at room temperature for 4 h. Removal of the solvent in vacuo afforded a viscous oil which was dissolved in benzene and extracted with 75 ml of aqueous HCl (8 N). The aqueous layer was then reextracted (2 × 100 ml) with benzene. Evaporation of the organic extracts in vacuo yielded a white solid. This solid was dissolved in acetone (25 ml) and treated with 1 ml of concentrated NH_4OH (0.015 mol) in the usual manner and then ether (50 ml) was added. After standing at room temperature for 24 h, the precipitated ammonium salt of the monoester was collected and dried in vacuo at 35 °C for 24 h, 2.2 g (81.2%), mp 182–184 °C. The sample was identical in all respects with that previously identified.

Di(2-naphthyl) Phenylphosphonate (5). This diaryl ester was prepared by an adaptation of a literature procedure for dialkyl phosphonates.[11a] A slurry of 2.3 g (55.6% in mineral oil, 0.053 mol) of NaH in 75 ml of anhydrous ether at room temperature was treated (dropwise) with 7.6 g (0.053 mol) of 2-naphthol in 50 ml of ether, and the resulting mixture was stirred at room temperature for 1 h. Treatment of this sodium aryloxide–ether mixture with 4.9 g (0.025 mol) of phenylphosphonic dichloride in 50 ml of ether afforded a clear solution. After addition, this solution was boiled (24 h), cooled to room temperature, and hydrolyzed (25 ml of saturated NH_4Cl solution) to remove unreacted aryloxide. The layers were separated and the aqueous layer was extracted (2 × 50 ml) with ether. The dried ($MgSO_4$) organic extracts were evaporated in

vacuo to give a white solid. Recrystallization of this solid from C_6H_6–C_6H_{12} (1:3) afforded 3.1 g (30.1%) of the diester **5**: mp 129–131 °C; ir[18] (KBr) ν 1620, 1592 (aromatic), 1260, 1238, 1205, 1150, 1115, 1027, 963, 937, 885, 862, 849, 815, 752, 739, 696, and 640 cm^{-1}; ^1H NMR ($DCCl_3$) δ 7.06–7.84 (m, 2 $C_{10}H_7$ and C_6H_5, 17 H), 8.05 (m, C_6H_5 2 H); ^{31}P NMR ($DCCl_3$ + pyridine) −11.34 ppm relative to 85% H_3PO_4; mass spectrum (70 eV) *m/e* 410 (M^+). Peak matching for $C_{26}H_{19}O_3P$: 410.107175. Found: 410.128523. The ester is insoluble in H_2O and was recovered unchanged after being stirred in 8 N HCl for 3 h.

Registry No.—**2** (R = C_6H_5), 824-72-6; **2** (R = c-C_6H_4), 1005-22-7; **2** (R = n-C_3H_7), 4708-04-7; **2** (R = 2-C_3H_7), 1498-46-0; **2** (R = $ClCH_2$), 1983-26-2; **2** (R = CH_3), 676-97-1; **4** (R = C_6H_5; Ar = p-$O_2NC_6H_4$), 57885-61-7; **4** (R = C_6H_5; Ar = 2-$C_{10}H_7$), 57885-62-8; **4** (R = c-C_6H_4; Ar = p-$O_2NC_6H_4$), 57885-63-9; **4** (R = n-C_3H_7, Ar = p-$O_2NC_6H_4$), 57885-64-0; **4** (R = n C_3H_7, Ar = 2-$C_{10}H_7$), 57885-65-1; **4** (R = C_6H_5; Ar = p-$O_2NC_6H_4$) free acid, 57072-35-2; **4** (R = 2-C_3H_7; Ar = p-$O_2NC_6H_4$), 57885-66-2; **4** (R = 2-C_3H_7; Ar = 2-$C_{10}H_7$), 57885-67-3; **4** (R = $ClCH_2$; Ar = p-$O_2NC_6H_4$), 57885-68-4; **4** (R = $ClCH_2$; Ar = 2-$C_{10}H_7$), 57885-69-5; **4** (R = CH_3; Ar = p-$O_2NC_6H_4$), 57885-70-8; **4** (R = CH_3; Ar = 2-$C_{10}H_7$), 57885-71-9; **5**, 57885-72-0; dimethylformamide, 68-12-2; p-nitrophenol, 100-02-7; 2-naphthol, 135-19-3.

References and Notes

(1) Journal paper no. 5976 of the Agriculture Experiment Station, Purdue University. This work was supported in part by National Institutes of Health Training Grant GM 1195 from the National Institute of General Medical Sciences and the USPHS, Grant CA 10367-06 (to K.D.B.) from the National Institute of Cancer. We (K.D.B.) also acknowledge the National Science Foundation grant to purchase the XL-100(15) NMR unit, Grant NSF GP-17641. L.G.B. is a recipient of a Research Career Development Award (GM 46404) from the U.S. Public Health Service.

(2) (a) Research Associate in Chemistry, 1973–1975; (b) Research Associate in Biochemistry, 1974–1975.

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(10) For a brief discussion on the synthesis of phosphonates, see G. M. Kosolapoff, "Organophosphorus Compounds", Wiley, New York, N.Y., 1950, Chapter 7, and references cited therein. Diesters may also be prepared by a variety of methods analogous to the synthesis of phosphate triesters; see E. Cherbuliez, "Organic Phosphorus Compounds", Vol. 6, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1973, Chapter 15.

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(14) (a) Obtained in water; see M. L. Nielsen, J. V. Pustinger, Jr., and J. Strobel, *J. Chem. Eng. Data*, **9**, 167 (1964). (b) Obtained in water; see J. G. Riess, J. R. Van Wazer, and J. H. Letcher, *J. Phys. Chem.*, **71**, 1925 (1967).

(15) For a brief discussion on the effects of charge (generally negligible), electronegativity of other atoms, and configurational changes on the ^{31}P resonance of phosphorus moieties, see ref 12.

(16) The conversion of **6** to **10** in the absence of 2-$C_{10}H_7OH$ is necessitated by the appearance of only the two ^{31}P resonances, −1.0 and +1.0 ppm (sample C, Table III) after 10 min mixing. These same resonances are also present in the absence of both pyridine and 2-$C_{10}H_7OH$; see Table IV.

(17) The interaction of DMF and $POCl_3$ has been extensively investigated by nuclear magnetic resonance in the last decade. A few of the conclusions are (1) that the major cationic formylating specie has the tentative structure $(CH_3)_2NCHCl^+$ with the anion being either $^-O_2PCl_2$ or Cl^-; (2) extensive heteronuclear decoupling experiments on ^1H have shown that there is no P–OCH covalent structure to the intermediate cation. For more detailed discussion, see (a) G. J. Martin and S. Poignant, *J. Chem. Soc., Perkin Trans. 2*, 642 (1974); (b) S. Alummi et al., *ibid.*, 2070 (1972); (c) G. J. Martin and S. Poignant, *ibid.*, 1964 (1972); (d) G. J. Martin, S. Poignant, M. L. Filleux, and M. T. Quemeneur, *Tetrahedron Lett.*, 5061 (1970); (e) G. Martin and M. Martin, *Bull. Soc. Chim. Fr.*, 1637 (1963), and references cited therein.

(18) Owing to the complexity of the infrared spectra, detailed interpretations were not attempted.

A One-Step Synthesis of Epoxyphosphonates

Bleecker Springs and Paul Haake*

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

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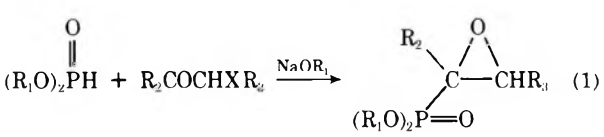
Owing to the recent interest in epoxyphosphonates generated by the newly discovered antibiotic fosfomycin, we have synthesized some epoxyphosphonates, $(R_1O)_2P(O)\overline{CR_2–O–CHR_3}$, by a facile one-step procedure. Our synthesis proceeds by the reaction of a stoichiometric amount of a dialkyl phosphonate, an α-halo ketone, and sodium alkoxide; the yields include (R_1, R_2, R_3, % yield) CH_3, CH_3, H, 84; C_2H_5, CH_3, H, 83; CH_3, $(CH_3)_3C$, H, 87. In addition, for the reaction with R_1 = CH_3, R_2 = CH_3, and R_3 = H, we have NMR evidence, a doublet at τ 8.5 (J_{PCCH} = 15 Hz), which indicates that the reaction proceeds via a phosphonate halohydrin intermediate (eq 6).

The novel structure of the newly discovered antibiotic fosfomycin [**1**, (−)-(1*R*,2*S*)-1,2-epoxypropylphosphonic acid] has generated interest in epoxyphosphonates.[1,2] Previous studies on epoxyphosphonates have been concerned primarily with either their potential as synthetic intermediates[3] or the mechanism of the reaction of dialkyl phosphonates, $(RO)_2P(O)H$, with α-halo ketones.[4] The discovery of fosfomycin and its mode of action as an analogue of phosphoenol pyruvate in its inhibition of the enzyme pyruval transferase has given epoxyphosphonates biochemical significance.[5]

We have synthesized epoxyphosphonates **2**–**8** by a facile, one-step procedure by the action of sodium alkoxide on a dialkyl phosphonate and an α-halo ketone (eq 1). In addition, we have NMR evidence concerning the mechanism of this reaction.



(1)

1-8

Experimental Section

We used the following instruments: Varian A-60 for NMR spectra, tetramethylsilane as internal standard; Perkin-Elmer 137 for infrared spectra; Hitachi RMU-6L for mass spectra. Analyses were determined by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Materials. Chloroacetone and 2-chloro-4,4-dimethyl-3-pentanone were prepared by treating acetone and ethyl *tert*-butyl ketone, respectively, with sulfuryl chloride.[6,7] Chlorocyclohexanone and 1-chloro-3,3-dimethyl-2-butanone were prepared by the reaction

Table I. Yields of Epoxyphosphonates

Compd	R_1	R_2	R_3	Yield, %
1	H	H	CH_3	
2	CH_3	CH_3	H	84
3	C_2H_5	CH_3	H	83
4	$C_6H_5CH_2$	CH_3	H	48
5	CH_3	$(CH_3)_3C$	H	87
6	CH_3	$(CH_3)_3C$	CH_3	70
7	CH_3	CH_3	CH_3	53
8	CH_3	$(CH_2)_4$		33

of cyclohexanone and pinacolone, respectively, with Cl_2.[8,9] α-Chloroacetophenone and 3-bromo-2-butanone (Aldrich) were used as received. Ethyl *tert*-butyl ketone was prepared by chromic acid oxidation of 2,2-dimethyl-3-pentanol.[10] Dimethyl and diethyl phosphonate (Aldrich) were used as received for synthetic reactions; dimethyl phosphonate was distilled, bp 170–171 °C, for kinetic experiments.

Dimethyl 1,2-Epoxy-2-propylphosphonate (2). The following is illustrative for the synthesis of all epoxyphosphonates described below. A solution of sodium methoxide was prepared by dissolving 0.06 mol (1.37 g) of sodium in 25 ml of methanol. The sodium methoxide was then added dropwise over a period of 15 min to a mixture of 0.06 mol (5.55 g) of chloroacetone and 0.06 mol (6.60 g) of dimethyl phosphonate in 5 ml of methanol at room temperature. After stirring for 1 h the solution was filtered, distilled to remove methanol, and refiltered. Ether was then added to precipitate any remaining sodium chloride. The solution was filtered again and ether evaporated off. A short-path distillation gave **2**: bp 75–76 °C (0.7 mm); mol wt 166 by mass spectroscopy; ir (neat) 1260 (P=O), 1235 (epoxide), 1185 and 1035 ($POCH_3$), 855, 835, and 760 cm^{-1} (epoxide); NMR ($CDCl_3$) τ 8.52 (d, 3 H, J_{PCCH_3} = 11.3 Hz), 7.31 (t, 1, J_{HCH} = 5.0, J_{PCCH} = 5.0 Hz), 6.91 (t, 1, J_{HH} = 5.0, J_{PCCH} = 5.0 Hz), 6.21 (d, 6, J_{POCH} = 11.0 Hz).

Anal. Calcd for $C_5H_{11}O_4P$: C, 36.15; H, 6.69. Found: C, 35.74; H, 6.92.

Diethyl 1,2-epoxy-2-propylphosphonate (3): bp 69–72 °C (0.5 mm) [lit.[4] 75 °C (0.6 mm)]; mol wt 194 by mass spectroscopy; ir (neat) 1260 (P=O), 1225 (epoxide), 1170 and 1030 (POC_2H_5), 855, 800, and 750 cm^{-1} (epoxide); NMR ($CDCl_3$) τ 8.69 (d, 3, J_{PCCH_3} = 11.3 Hz), 8.54 (t, 6, $J_{H_2CCH_3}$ = 7 Hz), 7.29 and 6.90 (t, 1, J_{HH} = 5.0, J_{PCCH} = 5.0 Hz), 5.82 (qq, 4, $J_{H_3CCH_2}$ = 7.0, J_{POCH} = 7.0 Hz).

Dimethyl 1,2-epoxy-3.3-dimethyl-2-butylphosphonate (5) was made starting from pinacolone: bp 75–77 °C (0.75 mm); mol wt 208 by mass spectroscopy; ir (neat) 1260 (P=O), 1235 (epoxide), 1185 and 1050 ($POCH_3$), 870, 830, and 750 cm^{-1} (epoxide); NMR ($CDCl_3$) τ 8.91 [s, 9, $(CH_3)_3C$], 7.15 and 7.01 (t, 1, J_{HCH} = 5.0, J_{PCCH} = 5 Hz), 6.21 (d, 6, J_{POCH_3} = 10.5 Hz); NMR (neat) two triplets become a doublet at τ 7.09 (J_{HCH} = 5 Hz).

Anal. Calcd for $C_8H_{17}O_4P$: C, 46.16; H, 8.23. Found: C, 45.95; H, 8.14.

Dimethyl 2,3-epoxy-4,4-dimethyl-3-pentylphosphonate (6) was made from 2-chloro-4,4-dimethyl-3-pentanone: bp 75–77 °C (0.75 mm); mol wt 222 by mass spectroscopy; ir (neat) 1260 (P=O), 1220 (epoxide), 1185 and 1030 ($POCH_3$), 835, 810, and 755 cm^{-1} (epoxide); NMR ($CDCl_3$) τ 8.92 [s, 9, $(CH_3)_3C$], 8.49 (d, 3, J_{HCCH_3} = 5.5 Hz), 6.22 (d, 6, J_{POCH} = 10.5 Hz).

Anal. Calcd for $C_9H_{19}O_4P$: C, 48.66; H, 8.64. Found: C, 48.68; H, 9.06.

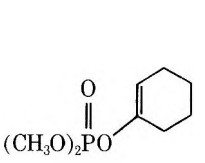
Compounds **4**, **7** and **8**, although new, were not verified by elemental analysis. **Dibenzyl 1,2-epoxy-2-propylphosphonate (4)** was prepared by the addition of sodium benzyloxide to dibenzyl phosphonate and chloroacetone in benzene. After filtration benzyl alcohol was removed by distillation. The pot residue containing **4** was passed through two silica gel columns for purification. The first column was eluted with benzene–chloroform–methanol (10:14:1) and the second column 15:15:1. Fractions with the appropriate NMR for the epoxide also have peaks in the NMR due to an impurity, probably $PhCH_2OH$. NMR ($CDCl_3$) τ 8.55 (d, 3, J_{PCCH_3} = 11.3 Hz), 7.40 and 6.93 (t, 1, J_{HCH} = 5.0, J_{PCCH} = 5.0 Hz, CH_2), 4.95 (d, 3, J_{POCH_2} = 8 Hz), 2.69 (s, 17, C_6H_5), 5.48 (s, 1.5, impurity). **Dimethyl 2,3-epoxy-2-butylphosphonate (7)** was made from 3-bromo-2-butanone: bp 59–62 °C (0.7 mm); ir (neat) 1260 (P=O), 1185 and 1030 ($POCH_3$), 855, 833, and 760 cm^{-1} (epoxide); NMR ($CDCl_3$) τ 8.65 (two doublets for cis and trans, 2, J = 5.5 Hz, $CHCH_3$), 8.55 (d, 3, J = 11.3 Hz, CH_3), 6.60 (qq, 1, J_{HH} = 5.5, J_{PCCH} = 5.5 Hz, $CHCH_3$), 6.23 [d, 7, J_{POCH} = 10.5 Hz, $P(OCH_3)_2$]; mass spectrum *m/e* 180. The analysis was low in carbon. **Dimethyl 1,2-epoxy-1-cyclohexylphosphonate (8)** was made from chlorocyclohexanone. The reaction mixture after distillation appeared by NMR to give a 50:50 mixture of the epoxyphosphonate **8** and dimethyl cyclohexenyl phosphate **9** (total yield of 66%): bp 84–87 °C (0.25 mm); ir (neat) 1670 (C=C), 1260 (P=O), 1190 and 1020 ($POCH_3$), 850, 830, and 785 cm^{-1} (epoxide); NMR (neat) τ 8.8–7.7 (m, 8, cyclohexyl), 6.65 (m, 1, epoxide), 6.21 (d, 6, J_{POCH} = 10.5 Hz), 4.5 (m, 1, vinyl proton).

Reaction of α-Chloroacetophenone with Dimethyl Phosphonate. In an attempt to make the corresponding epoxide, dimethyl 1,2-epoxy-2-phenyl-2-ethylphosphonate, the only apparent product by NMR was the vinyl phosphate **10.** No attempt was made to isolate this product.

Results

Our synthetic method (eq 1) is a modification of two previously existing methods: reaction of a phosphonate halohydrin with base to give the epoxide, and reaction of a sodium dialkylphosphonate with an α-chloro ketone. The yields are in Table I.

This reaction appears to give only the epoxide with aliphatic α-halo ketones. The reaction of α-chloroacetophenone with dimethyl phosphonate gave only dimethyl 1-phenylvinylphosphate. Attempts to form the epoxide from the corresponding phosphonate halohydrin also resulted in the formation of **10.** However, the addition of sodium diethylphosphonate to α-chloroacetophenone has been reported to give a mixture of the benzyl epoxide and the vinyl phosphate.[11] The reaction of chlorocyclohexanone with dimethyl phosphonate appeared by NMR to give an equimolar ratio of the epoxide **8** and the vinyl phosphate **9.**



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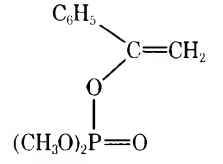

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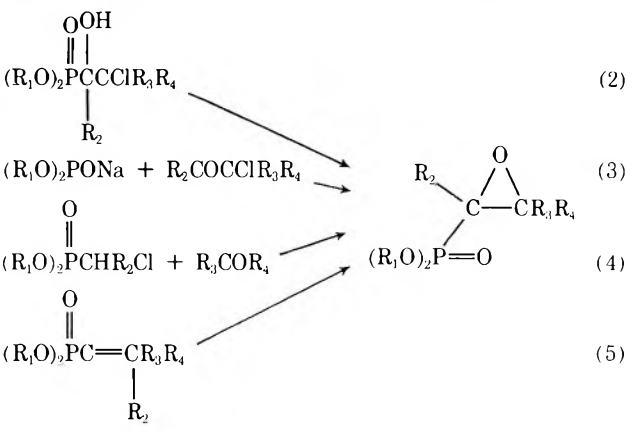
NMR Spectra of the Synthetic Reaction. The reaction solution for the synthesis of dimethyl 1,2-epoxy-2-propylphosphonate was made up as described and the NMR spectra in Figure 1 were obtained after successive additions of 0.25 equiv of sodium methoxide. The CH_3 group in chloroacetone is replaced by two doublets at τ 8.5; the one with the larger coupling is due to the halohydrin and the one with the smaller coupling is due to epoxyphosphonate. These assignments are based on spectra of authentic samples of each.

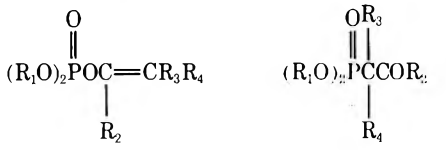
Discussion

Epoxyphosphonate Synthesis. Present methods for the synthesis of epoxyphosphonates have recently been reviewed.[12] These methods include (a) the reaction of a dialkyl phosphonate halohydrin with base (eq 2); (b) the reac-



tion of a sodium dialkylphosphonate with an α-halo ketone (eq 3); (c) Darzen's reaction of dialkyl chloromethylphosphonates with carbonyl compounds (eq 4); and (d) direct epoxidation of unsaturated phosphonates with a peroxide and catalyst or a peracid (eq 5).

In general the yields for these reactions are at best 60–70%. In addition, they are subject to limitations. (a) The reaction of a sodium dialkylphosphonate has been reported to also give the isomeric enol or vinyl phosphate **11** and β-ketophosphonate **12**;[11,13] the α-halo carbon cannot be tertiary.[13] (b) The Darzen's reaction is without side reactions, but is limited to ketones and aryl aldehydes; R_3 and R_4 = alkyl or R_4 = aryl and R_3 = H; in addition, this reaction has, as yet, been carried out only with the methyl and ethyl esters of chloromethylphosphonic acid (R_2 = H). (c) Epoxidation of the unsaturated phosphonate can result in side reactions: in a buffered solution trifluoroperacetic acid, when used as the oxidant, may cause ring opening of the epoxide when formed,[14] and the use of *tert*-butyl peroxide has been shown to result in the Michael addition product **13** of the butoxide to the olefin.[3] (d) Epoxidation has two



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12

13

distinct advantages. First, the formation of the intermediate, unsaturated phosphonate in the synthetic sequence permits an acid-catalyzed ester hydrolysis prior to epoxidation. Once the epoxide is formed, as in the other reactions discussed, the esters can be removed by hydrogenation if $R_1 = CH_2C_6H_5$.[15] Second, if R_3 or $R_4 \neq H$, then there will be two isomeric unsaturated phosphonates formed which can be separated. Epoxidation of the appropriate isomer can then take place in the presence of a resolving agent in order to isolate the product with the desired absolute stereochemistry.[16]

In our attempt to synthesize analogues of fosfomycin, our attention was directed to the reaction of a phosphonate halohydrin with base. Phosphonate halohydrins are readily formed from the reaction of a dialkyl phosphonate with an α-chloro ketone,[13,17,18] so we examined the reaction of chloroacetone and dimethyl phosphonate with 1 equiv of sodium methoxide. The addition of 1 equiv of sodium methoxide to the reactants resulted in the immediate precipitation of sodium chloride. After stirring for 1 h, an NMR spectrum indicated the presence of only the epoxide. Refinement of the reaction work-up has led to reproducible yields of 84% for both **2** and **3**. These yields represent a significant improvement over the yields of 30 and 63% reported for the one-step reaction of chloroacetone with sodium diethyl phosphonate.[4,13] This procedure avoids formation of the sodium dialkyl phosphonate salt which tends to precipitate out and coat the sodium as it dissolves in a solution of the dialkyl phosphonate in ether.[4] We have extended this reaction to a variety of α-halo ketones and two other phosphonates. The procedure seems facile and convenient.

Esterification of fosfomycin causes a marked decrease in its biological activity.[15] The synthesis of any analogue therefore requires the free acid as a final product. Since it has been shown that a dibenzyl epoxyphosphonate can be hydrogenated to give the free acid,[15] we extended our reaction to include that of chloroacetone with dibenzyl phosphonate; although we did not succeed in preparing an analytical sample, free from benzyl alcohol, the NMR demonstrated that this method is successful with benzyl esters.

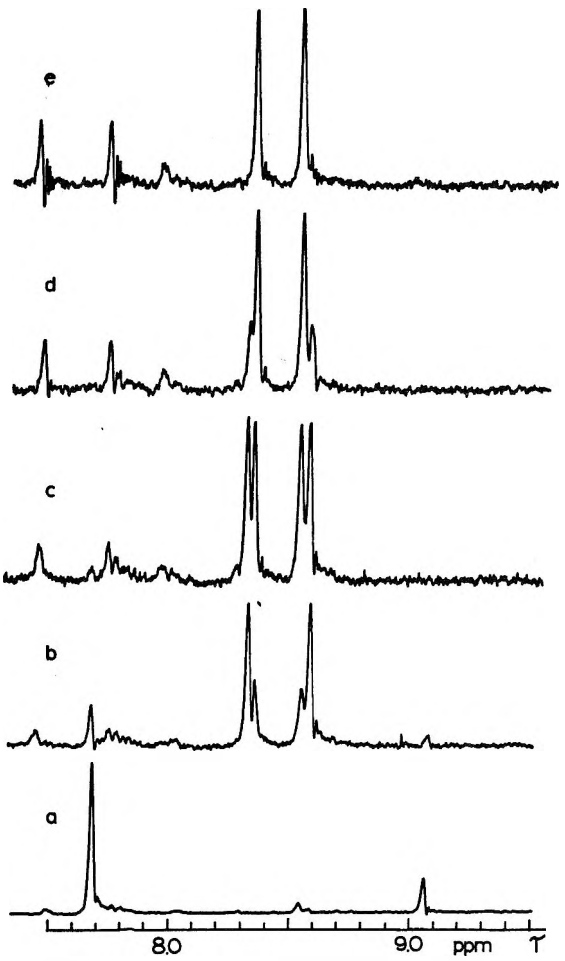
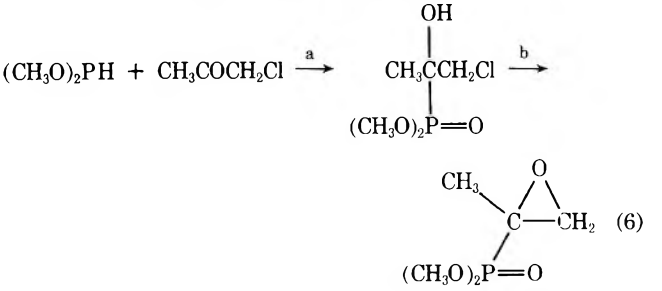


Figure 1. NMR spectra of chloroacetone and dimethyl phosphonate before (a) and after the addition of 0.25 (b), 0.50 (c), 0.75 (d), and 1.0 (e) equiv of sodium methoxide.

Mechanism of the Reaction. The NMR spectra in Figure 1 indicate that the reaction proceeds by a two-step mechanism (eq 6) through the chlorohydrin; the outer doublet at τ 8.5 (J = 15 Hz) is due to the splitting of the methyl group in the phosphonate halohydrin by the phosphorus. The inner doublet (J = 11.3 Hz) is due to the splitting of the methyl group of the epoxide by the phosphorus. Therefore, the spectra demonstrate formation and disappearance of chlorohydrin as sodium methoxide is added.

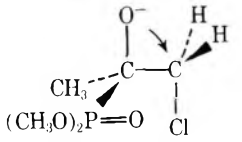


(6)

Formation of the vinyl phosphate in the case of both α-chloroacetophenone and α-chlorocyclohexanone is not unexpected. The similar reaction of sodium dialkyl phosphonates with α-halo ketones has been reported to give the epoxide alone, the vinyl phosphate alone, a mixture of the epoxide and vinyl phosphate, or a mixture of the epoxide

and β-ketophosphonate.[4,11,13] Similarly, the reactions of trialkyl phosphites with α-halo ketones give a variety of products depending on reaction conditions. Investigations of the mechanism of these reactions have led to little conclusive evidence about their mechanism.[19] Formation of the vinyl phosphate, epoxyphosphonate, and phosphate halohydrin is believed to result from attack by the phosphorus at the carbonyl carbon. Formation of the β-ketophosphonate results from attack at the α-halo carbon.

For the aliphatic α-halo ketones, formation of the epoxide is the favored course of the reaction. The phosphorus can attack the carbonyl carbon to form the intermediate halohydrin. The α carbon is free to rotate around its bond to the carbonyl carbon, positioning the halide trans to the oxygen which is involved in nucleophilic attack.



In the case of chlorocyclohexanone, the α carbon is not free to rotate. The preferred conformation of the molecule has the chlorine in an equatorial position. Attack by the phosphorus can result in chlorohydrin with hydroxyl and chlorine having either cis or trans stereochemistry; the trans can lead to epoxide through the axial–axial conformer (which has the phosphonate group equatorial), but the cis isomer cannot achieve the proper stereochemistry to generate epoxide so it would give vinyl phosphate by attack at phosphorus; we found a 50:50 mixture of epoxyphosphonate and vinyl phosphate.

For α-chloroacetophenone, the α carbon is free to rotate in epoxide formation. However, attack of the oxygen at phosphorus is also favorable owing to the formation of a conjugated system. Meisters and Swan, who found that sodium diethylphosphonate and α-chloroacetophenone in liquid ammonia gave a mixture of the epoxide and vinyl compounds, suggested that the polarity of the solvent was the determining factor.[11] They proposed that a more polar solvent would favor epoxide formation; however, our reaction in methanol gives no epoxide.

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Registry No.—**2**, 36432-35-6; **3**, 1445-84-7; **4**, 58074-07-0; **5**, 58074-08-1; **6**, 58074-09-2; **7**, 58074-10-5; **8**, 13176-31-3; chloroacetone, 78-95-5; 2-chloro-4,4-dimethyl-3-pentanone, 40955-58-6; chlorocyclohexane, 822-87-7; 1-chloro-3,3-dimethyl-2-butanone, 13547-70-1; α-chloroacetophenone, 532-27-4; 3-bromo-2-butanone, 814-75-5; dimethyl phosphonate, 868-85-9; diethyl phosphonate, 762-04-9; sodium methoxide, 124-41-4; sodium benzyloxide, 20194-18-7; dibenzyl phosphonate, 17176-77-1.

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Conformation and Electronic Structure of the Lithium Adduct of Methylenephosphoranes

Thomas A. Albright* and E. E. Schweizer*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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NMR evidence is presented to show that lithium adducts are formed upon addition of *n*-butyllithium to methyltriphenylphosphonium iodide. The geometry of the lithium adduct to methylenephosphorane was examined by means of CNDO/2 molecular orbital calculations. The electronic structure of this molecule is compared to several other related molecules. The calculations suggest that the lithium does not perturb the electron distribution or conformation about the methylene group significantly compared to methylenephosphorane, with the exception that the phosphorus atom loses electron density in the adduct. Calculations of P–C couplings by the finite perturbation method support the proposed conformation.

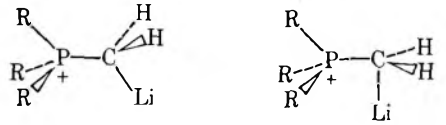
It has been previously established that lithium salts can bond to phosphorus–carbon ylides.[1] These compounds are the simplest type of a rich variety of organometallic compounds formed where the methylene carbanion of a phosphorus ylide bonds to a metal.[1a] However, there is very little reported on the nature of these adducts. From a proton NMR investigation it was proposed[1b] that the conformation of these lithium adducts was 1 since the C–H coupling of the methylene group was approximately the same as that found for phosphonium salts (see Table I). The C–H coupling for the salt-free ylide was, however, 15 Hz larger than that obtained for the lithium adduct.[1b] Evidence of both

Table I. NMR Properties of the Methylenephosphoranes and Their Related Salts[a]

Compd	Solvent	^{13}C chemical shift, ppm	^{31}P chemical shift, ppm	$^{1}J_{P-C}$, Hz[b]	$^{1}J_{C-H}$, Hz
$Me_3P{=}CH_2$[c]	C_6D_6	−1.5	2.1	90.5	149
$Ph_3P{=}CH_2$[d]		−4.1		100.0	153[e]
$Me_2EtP{=}CH_2$[f]	Neat				149
Me_3P^+-Me I^- [g]	$CDCl_3$	11.3	25.1	56.0	134[h]
Ph_3P^+-Me I^-	$CDCl_3$	11.4	21.1	57.1	
Ph_3P-CH_2Li I^-	C_6D_6–Et_2O 6:1	−4.1	22.1	51.9	133
	C_6D_6–Et_2O 1:1	−4.3	18.7	61.3	
	C_6D_6–Et_2O 1:6	−5.0		64.7	
Me_2EtP^+-CH_2Li Cl^-	C_6H_6				134

[a] The ^{13}C chemical shifts are relative to internal Me_4Si and refer to the methylene carbon (or methyl) carbon directly bonded to phosphorus. The ^{13}C and P–C couplings for the phenyl ring carbons in the different solvents for the lithium compounds are identical. [b] The digital resolution was ±0.1 Hz. [c] Values taken from H. Schmidbaur, W. Buchner, and D. Scheutzow, *Chem. Ber.*, **106**, 1251 (1973). [d] Y. Yamamoto and H. Schmidbaur, *J. Organomet. Chem.*, **97**, 479 (1975). [e] K. A. O. Starzewski and M. Feigl, *ibid.*, **93**, C20 (1975). [f] H. Schmidbaur and W. Tronich, *Chem. Ber.*, **101**, 3556 (1968). [g] W. McFarlane, *Proc. R. Soc., London, Ser. A*, **306**, 185 (1968). [h] I. J. Petracek et al., *Tetrahedron Lett.*, 707 (1970).

experimental and theoretical nature is presented that indicates that structure **2** is a possible conformation of these



1 **2**

2a, R = H

lithium adducts. Furthermore, lithiated phosphoranes are always likely to be obtained when alkyllithium compounds are employed to generate methylenephosphoranes (and possible other nonstabilized phosphoranes), even under "salt-free" [2] conditions. This casts doubt on the validity of kinetic and stereochemical investigations with nonstabilized (ylides that do not contain electron-withdrawing groups on the carbon bearing the formal negative charge) phosphoranes.[3]

Results and Discussion

The ^{13}C NMR of methylenetriphenylphosphorane along with those of several other ylides has previously been published.[4a] We now wish to correct that NMR data in light of our current findings, i.e., the previously reported ^{13}C chemical shifts and ^{31}P–^{13}C couplings for "methylenetriphenylphosphorane" are, in fact, those for the lithium adduct of the ylide. Listed in Table I are several NMR parameters that provide strong evidence for the formation of lithium salts from their corresponding ylides (for the preparation of the triphenyl substituted compounds, see the Experimental Section). That the compounds generated by the reaction of *n*-butyllithium with methyl phosphonium salts are not ylides is evidenced by the following facts.

1. The C–H coupling for the methylene group is essentially identical for the triphenyl- and dimethylethylmethylenephosphorane lithium adducts. However, the C–H coupling for methylenetrimethyl- and dimethylethylphosphorane, prepared by a desilyation process,[4b] is 15 Hz larger.

2. The directly bonded P–C coupling for the triphenyl substituted lithium compound is similar to that found for methyltriphenyl- and tetramethylphosphonium iodide. Methylenetrimethyl- (or triphenyl-) phosphorane, however, has a P–C coupling of 48.1–25.8 Hz larger than that found for the lithiated compound.[5]

3. The P–C coupling is strongly dependent on the concentration of ether as a solvent, implying coordination of lithium to the ether (vide infra).

4. The ^{31}P chemical shift of methylenetrimethylphosphorane is 2.1 ppm, shielded by 23.0 ppm from its phosphonium salt protomer. This is normal for nonstabilized ylides.[6] On the other hand, there is essentially no difference between the ^{31}P chemical shifts of the lithiated triphenylphosphorane and its phosphonium salt. The ^{31}P chemical shift of methylenetriphenylphosphorane in Me_2SO[6] and benzene[7] has been reported as 22.2 and 22.3 ppm, respectively, and thus (note the similarity with the phosphonium salt chemical shift) also provides evidence that the compound in these solvents is not the ylide, but rather the lithium adduct.

If the ^{31}P chemical shifts can be related in a qualitative sense to the electronic environment of the phosphorus nucleus,[8,9] then these data suggest that the phosphorus in the phosphonium salts and the lithium adducts is somewhat similar. The ^{13}C chemical shifts indicate substantial electron density on the carbon adjacent to the lithium which is comparable to that found for methyllithium (−11 to −15 ppm)[10] and methylenetrimethylphosphorane.

The conformation and electronic structure of the lithium adduct of methylenephosphorane was studied by CNDO/2 molecular orbital calculations.[11] Figure 1 shows the four

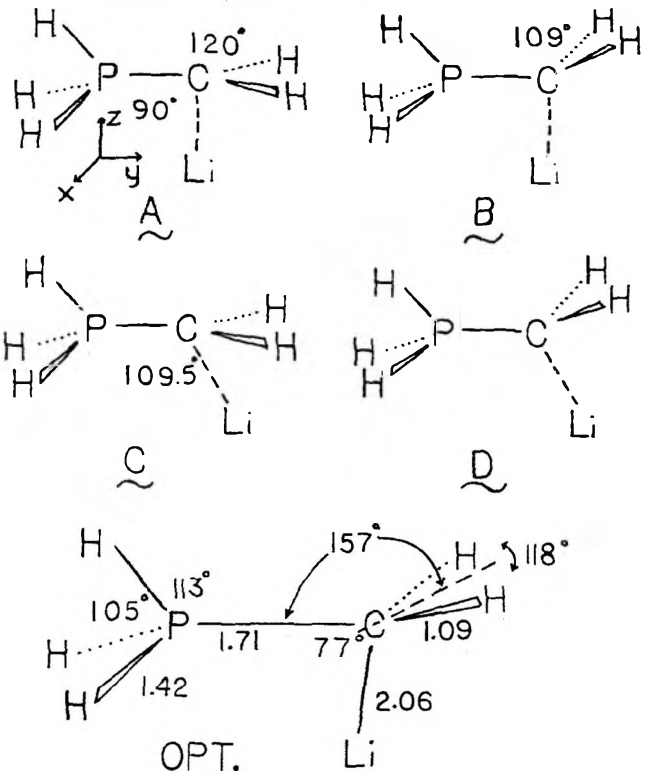


Figure 1. The paths of approach of a lithium cation to methylenephosphorane and the final optimized structure.

paths of approach for a lithium cation considered, as well as the final geometry optimized structure. Figure 2 shows the relative energies (using the spd basis set) for these paths. It is seen that there is a marked tendency for lithium

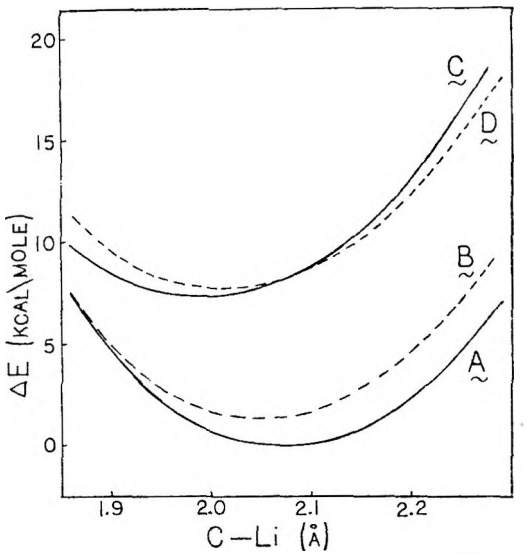


Figure 2. The relative energies of the lithium adduct with respect to the C–Li bond distance and the possible paths considered in Figure 1. The C–P bond distance is held constant at 1.68 Å. The letters refer to the paths considered in Figure 1.

to form a P–C–Li bond angle of 90°. This is analogous to the lithium complex of formaldehyde[12] as determined by ab initio molecular orbital calculations and underscores the ability of the phosphonium group to form σ_π type bonds both with and without d orbitals.[14] The CNDO/2 spd parameterization has given reliable geometries for phosphorus-containing molecules;[14-16] however, the CNDO/2 and INDO methods give bond angles with lithium that seem to be rather smaller than expected.[17] The difference in energy between the optimized structure in Figure 1 and one with a P–C–Li bond angle of 90° and the methylene group flattened onto the X–Y plane (**2a**) is only 3.5 kcal/mol. This probably represents a better fit (in accord with the NMR evidence and theoretical calculations thereof, described below) to the conformation of the lithiated phosphoranes in solution. The calculations do not take into account solvent–solute interactions; however, solvent coordination effects with lithium are mimicked below. The CNDO/2 method without d orbitals gives erroneously long P–C bond lengths,[14,15] so a geometry optimization with this basis set was not attempted.

The electron distribution for the lithium adduct of methylenephosphorane, the parent ylide, and its phosphonium cation is given in Figure 3. It is well known that the CNDO/2 level of approximation with a spd basis set overemphasizes d orbital importance,[18] so that deleting the d orbitals from the basis set will effectively bracket the "real" situation (the charges from the sp basis set are given in parentheses). The charges for methylphosphonium cation, **3**, and methylenephosphorane, **4**, represent those from totally optimized structures.[13] Molecular orbital calculations of a semiempirical, as well as ab initio, nature on **4** using assumed geometries have been previously published.[19] The charge distribution with and without d orbitals in Figure 3 is similar to these previous calculations.

There are several details that merit attention in comparing the charges for the molecules in Figure 3. The carbon in **2a** loses only a small amount of charge compared to the ylide **4**. This is in accord with the similarity of the ^{13}C

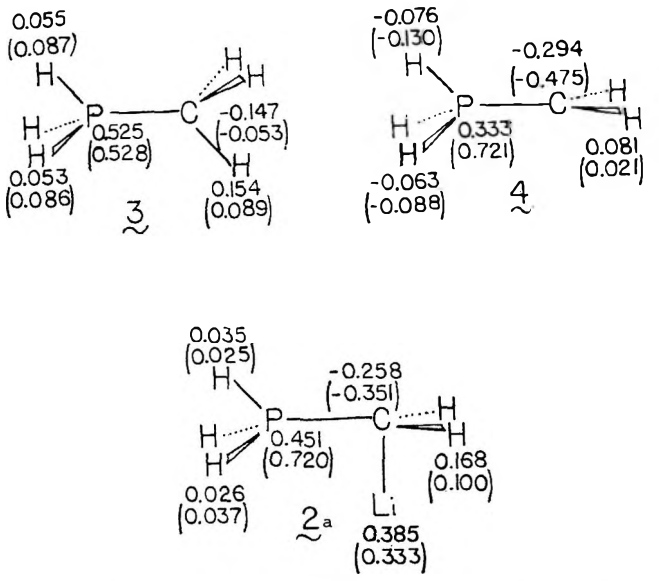
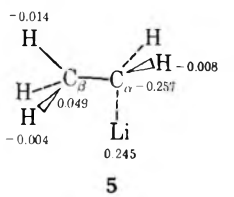


Figure 3. Electron distribution in the lithium adduct of methylenephosphorane and related molecules. The charges refer to those obtained with the spd basis set; those in parenthesis are from the sp basis set.

chemical shifts of the methylene carbons of methylenetrimethylphosphorane and the lithium adduct of methylenetriphenylphosphorane in Table I. The lithium atom also retains a good share of its positive charge. The major difference between the two basis sets is reflected on the charge on phosphorus for **2a**. The charge on phosphorus in the spd basis set approaches that of the phosphonium cation, **3**, which is consistent with the ^{31}P chemical shifts in Table I. The charge on phosphorus for **2a** (and **4**) is much too large in the sp basis set. The fact that phosphorus loses electron density in **2a** relative to **4** is a consequence of the lithium cation polarizing the molecule in a manner that alternates positive and negative charges relative to the site of substitution of the lithium.[20] This charge polarization effect is also apparent for the electron distribution in ethyllithium (using CNDO/2). The charge on the β carbon in the INDO approximation increases to 0.131 electrons while that for the lithium decreases to 0.207 (it might, therefore, be expected that the β carbon should be deshielded with respect to that of ethane in the ^{13}C NMR). For this calculation standard bond lengths and angles[21] were used with a C–Li bond distance of 2.05 Å.[22] The conformation of ethyllithium with a C–C–Li bond angle of 90° and C_α–C_β–H (H–C_α–H) bond angles of 109.47° (**5**) was 18.7 kcal/mol (17.8

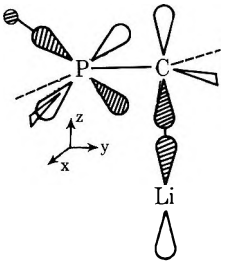


5

kcal/mol with INDO) more stable than that with a C–C–Li bond angle of 109.47°. The conformation with a H–C–H and C–C–Li bond angles of 120 and 90°, respectively (analogous to **2a**) was less stable than that in **5** by 25.7 and 30.6 kcal/mol by CNDO/2 and INDO calculations, respectively.

The highest occupied molecular orbital in **2a** (5a′) is comprised of a p_z orbital on carbon overlapping with a sp orbital on lithium and the d_{yz} orbital on phosphorus. This is the only molecular orbital that contains significant involvement of the orbitals of lithium. There are also several

low-lying unoccupied molecular orbitals consisting chiefly of d orbitals on phosphorus and p orbitals on lithium. The difference in the bond order between carbon and lithium, in **2a**, is 0.850 and 0.570 electrons (for the spd and sp basis sets, respectively) *less* than that in ethyllithium (using the CNDO/2 wave function). Therefore, the bonding between carbon and lithium in **2a** seems to lie between that of an ionic complex and a σ bond.



As a further check on the conformation of the lithium adduct of methylenephosphorane, the nuclear spin coupling of phosphorus to carbon was calculated by the finite perturbation method[23] using CNDO/2 wave functions.[24] This method has been shown to give reliable one-bonded P–C couplings for a variety of tetravalent phosphorus compounds.[14,26] The calculated P–C couplings in Table II are quite close to those given in Table I with the exception of the completely optimized structure of the lithium adduct of methylenephosphorane. A much better fit to the experimental values is found for **2a** where the P–C–Li bond angle is 90° and the methylene group lies in the xy plane (again, note that this conformation is only 3.5 kcal/mol less stable than the completely optimized one).[38] Any tipping of the methylene group out of this plane reduces the P–C coupling for both the lithium complex and methylenephosphorane[14] (the calculated P–C coupling for the structure analogous to **1** was −7.7 Hz). Note also that while all of the C–H couplings for **2a, 3,** and **4** are smaller than those in Table I (this is normal with CNDO/2[29]), their relative magnitudes are correctly predicted. These calculations include only the Fermi contact contribution to the nuclear spin couplings. The spin dipolar and orbital contributions are felt by the present authors to contribute to a neglible extent for $^1J_{P-C}$ in tetravalent phosphorus compounds. This rests, in part, on the fact that the calculated P–C couplings are accurate

Table II. Calculated P–C, C–H, C–C Couplings, and Valence Shell s Orbital Bond Orders[a]

Compd	$^1J_{P-C}$, Hz	P^2_{SpSc}	$^1J_{C-H}$, Hz
$H_3P{=}CH_2$	114.7	0.2942	121.4
$H_3P^+{-}CH_3$	45.6	0.2266	88.5
$H_3P^+{-}CH_2Li$ totally optimized	6.4	0.2178	85.6
2	38.5	0.2351	84.9
	$^1J_{C-C}$	P^2_{ScSc}	$^1J_{C-H}$
CH_3CH_2Li, C–C–Li = 90°			
5 (HCH = 109°, C–C–H = 109°)	6.5	0.1953	74.0[b]
HCH = 120°, C–C–H = 120°	40.3	0.2396	140.6[b]
CH_3CH_3[c]	41.5	0.2490	122.1

[a] The calculations for the phosphorus compounds are of the CNDO type and those of ethyllithium and ethane are from the INDO approximation. All couplings were calculated to be positive. [b] The C–H couplings are for the methylene group of ethyllithium. [c] Values taken from G. E. Maciel, J. W. McIver, Jr., N. S. Ostund, and J. A. Pople, *J. Am. Chem. Soc.*, 92, 1, 11 (1970).

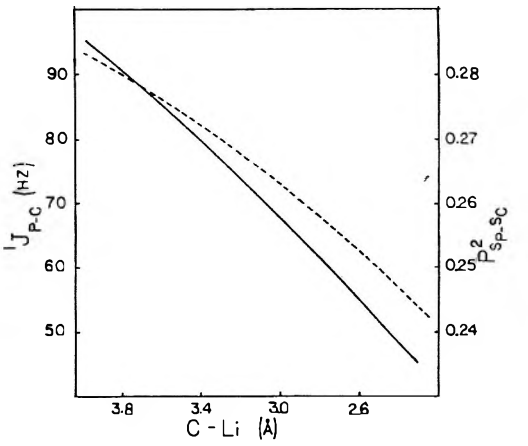


Figure 4. Calculated P–C couplings (solid line) and phosphorus 3s–carbon 2s bond orders (dashed line) as a function of the C–Li bond distance.

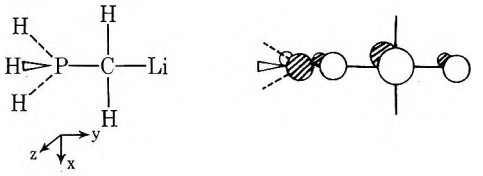
in comparison to the experimental values for many tetravalent phosphorus compounds.[14,26] Also, $^1J_{P-C}$ follows trends similar to those found for $^1J_{C-C}$;[14] spin orbital and dipolar contributions have been shown by theoretical calculations to be insensitive to variations of $^1J_{C-C}$.[29b]

A decrease in C–C coupling when the methylene group is tipped out of the xy plane is also evident for ethyllithium. Thus, the C–C coupling drops from 40.3 to 6.5 Hz when the methylene group is tipped 60° from the xy plane by the INDO method. The CNDO values (not listed in Table II) also reproduce this trend; however, the calculated C–C and C–H couplings are smaller by factors of approximately 1.5 and 0.6, respectively. Note that the calculated C–H coupling for ethyllithium (in **5**) is somewhat smaller than that reported for methyllithium (98 Hz).[27] The directly bonded C–Li coupling of ethyllithium (in **5**) calculated by INDO was +20.7 Hz (+11.7 Hz with CNDO/2) and is in moderately good agreement to that found for methyllithium (15 Hz)[27] and n-butyllithium (14 Hz).[28] The calculated C–Li coupling is too large for ethyllithium with all tetrahedral angles (25.4 Hz) and too small for the conformation with the methylene group in the xy plane (7.4 Hz). Since the INDO method has been found to be remarkably accurate in calculations of C–C (and C–H) couplings for a large variety of systems[29] and the CNDO/2 results for ethyllithium parallel these, the assignment of conformation **2a** for the lithium adduct of methylenephosphorane is strengthened (i.e., the decrease in $^1J_{C-C}$ with tipping of the methylene group does not appear to be sensitive to the basis set used).

It is well known that alkyllithium compounds, methyllithium in particular, exist as dimers or tetramers in solution.[22] This is probably not the case for the lithium adduct of methylenetriphenylphosphorane for two reasons. First, the bulky triphenyl groups would be expected to oppose this tendency for steric reasons. Secondly, the P–C–H bond angle would have to approach 109° if dimerization occurred which according to our finite perturbation results would produce a very small P–C coupling, similar to that calculated for the totally optimized structure in Table II which is not observed experimentally. However, the lone pairs of a solvent such as ether ought to be coordinated with the lithium. Increasing the amount of ether might be expected to increase the coordination of the lithium to ether at the expense of weakening the carbon–lithium bond. Therefore, the 12.8-Hz increase in the P–C coupling of the lithium adduct of methylenetriphenylphosphorane with increasing concentration of ether reported in Table I may be explained in this manner.[30] Other ylides that can be prepared and recrystallized in the absence of lithium salts such as

acetonylidenetriphenylphosphorane show no change in P–C couplings when the solvent and concentration was widely varied.[31] A similar solvent dependence of C–H coupling in benzyllithium has also been observed and discussed in terms of solvent coordination to the lithium.[32] To test the hypothesis that weakening the C–Li bond would increase the P–C coupling, a series of finite perturbation calculations were carried out on **2a**. The C–Li bond distance was decreased from 4.00 Å in steps of 0.25 Å with the P–C bond distance fixed at 1.68 Å (variations of the P–C bond distance in methylenephosphorane, for example, do not change the P–C coupling significantly[14]). The results of these calculations, as shown in Figure 4, agree nicely with this hypothesis. Furthermore, the s character in the C–H, C–C, and P–C bonds has been related to the C–H, C–C,[29] and P–C[26] couplings. It is evident from Figure 4 that the phosphorus 3s–carbon 2s bond order varies in an almost parallel manner to the calculated couplings. Therefore, this increase in the P–C coupling with respect to increasing C–Li bond distance is not a peculiarity of the finite perturbation method itself.

Finally, prompted by a report that ab initio calculations indicate that replacement of hydrogen for lithium atoms about methane remarkably stabilizes the square-planar conformation at carbon, relative to the tetrahedral one,[33] CNDO/2 calculations were carried out on the lithium adduct of methylenephosphorane to see if the molecule with a square-planar carbon might be stable. It was thought that the d_{YZ} orbital might appreciably interact with the highest occupied molecular orbital on a square planar carbon system thus stabilizing it (especially with the overemphasis of d orbitals in the CNDO/2 approximation), in a manner originally suggested by Hoffmann.[34] However, this conformation was found to be less stable by 65.7 and 69.3 kcal/mol relative to **2** with the spd and sp basis sets, respectively. Furthermore, this conformation was a saddle point on the energy surface, collapsing with no energy of activation to the optimized structure. Therefore, d orbitals on phosphorus provides only a 3.6 kcal/mol stabilization for the square planar carbon using the CNDO/2 approximation.



Conclusions

It is clear from the NMR evidence and theoretical calculations that the reaction of alkyllithium compounds with methyl-substituted phosphonium salts does not produce methylenephosphoranes, but rather, lithium salt adducts which possibly have the conformation **2**. Other nonstabilized ylides such as ethylidene- or ispropylidenetriphenylphosphorane apparently do not form stable lithium adducts judging from the ^{13}C NMR and ^{31}P–^{13}C coupling evidence[8,14] if the solutions are stirred *for at least 2 h* after the alkyllithium reagent is added and before the final filtration. Certainly the rate data collected for the reactions of methylenephosphoranes are likely to be erroneous.[35] The fact that betaine intermediates are isolated from nonstabilized ylides but not from stabilized ylides has led to some conclusions regarding the relationships of the rates of the various steps in the Wittig reaction.[3,36] These conclusions are likely to be suspect since a lithium cation can stabilize the betaine by coordination with the oxyanion, if other alkylidenephosphoranes do indeed *initially* form lithium salt adducts. Likewise, the differences in the stereochemistry of the Wittig reaction using stabilized and nonstabilized ylides[3,37] may have to be reexamined.

Experimental Section

The solutions of the lithium iodide adduct of methylenetriphenylphosphorane were prepared in a drybox by dropwise addition of an equimolar amount (2.7 ml) of *n*-butyllithium in hexane (Alfa Chemicals) to a suspension of 2.0 g of recrystallized methyltriphenylphosphonium iodide (Aldrich) in 20 ml of diethyl ether (dried and distilled over NaH). The resulting red solution was stirred for approximately 2 h and concentrated in vacuo. The red solid was dissolved with the solvent listed in Table I to a concentration of 0.5 M and filtered several times through a pipette packed with glass wool. A plug was inserted into the NMR tube and the top filled with wax. No decomposition of the lithium adduct of the ylide was observed by ^{13}C NMR after several days; likewise no precipitate formed in the tube after this period of time. The ^{13}C and ^{31}P NMR were obtained on a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system. The ^{13}C and ^{31}P NMR data were taken at operating frequencies of 22.63 and 36.43 MHz, respectively. All calculations were carried out with a Burroughs B6700 computer.

Acknowledgments. We wish to thank Dr. W. J. Freeman for obtaining the ^{13}C and ^{31}P NMR. A generous allocation of computer time from the University of Delaware is gratefully acknowledged.

Registry No.—$Ph_3{}^+PMe\ I^-$, 2065-66-9; $Ph_3P^+CH_2Li\ I^-$, 57454-94-1; butyllithium, 109-72-8.

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Metalation of Phosphine Imides with Organolithium Compounds

Clarence G. Stuckwisch

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

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Phenyllithium metalates triphenylphosphine *N*-phenylimide (**1a**) in the ortho position of a *P*-phenyl group and diphenylalkylphosphine *N*-phenylimides on the α carbon of the alkyl group. Alkyllithium reagents react with triphenylphosphine *N*-phenylimide to give the ortho-metalated imide in addition to a competitive reaction which involves an initial displacement of phenyl by alkyl followed by α-metalations on the alkyl carbon (**9a** and **9b**). Displacement of a phenyl group is more pronounced with methyllithium than with *n*-butyllithium. Halogen–metal exchange is not observed in the reaction of *n*-butyllithium with triphenylphosphine *N*-(4-bromophenyl)imide.

Metalation of triphenylphosphine by *n*-butyllithium gives, subsequent to carbonation, an 8% yield of 3-carboxyphenyldiphenylphosphine.[1] Phenylsodium and triphenylphosphine yield 10% 5-phenyldibenzophosphole, presumably through the intermediacy of an ortho-metalated compound.[2] Alkylithium compounds metalate benzyldiphenylphosphine[3] and alkyldiphenylphosphines[4] on the α-alkyl carbon, methyl hydrogen being more easily displaced than methylene hydrogen. Alkylphosphine oxides metalate easily on an α carbon.[5a,b] Gilman and Brown reported that triphenylphosphine oxide is not metalated by phenyllithium or phenylmagnesium bromide.[1] Seyferth et al.[6a,b] have shown that alkyl Grignard or alkyllithium reagents displace a phenyl group from triphenylphosphine oxide, ultimately yielding an α-metalated diphenylalkylphosphine oxide. They present evidence that the overall reaction takes place in two steps:

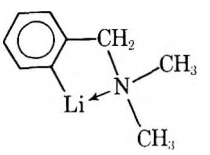
$$(C_6H_5)_3PO \xrightarrow{RCH_2Li} (C_6H_5)_2PO(CH_2R) + C_6H_5Li$$

$$(C_6H_5)_2PO(CH_2R) \xrightarrow{R'Li} (C_6H_5)_2PO(LiCHR) + R'H$$

$R' = C_6H_5$ or RCH_2

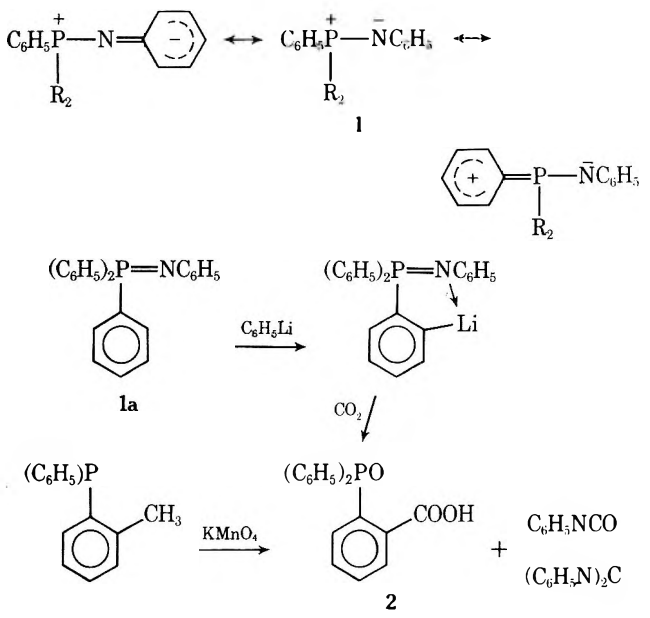
Similar results were observed with triphenylphosphine sulfide.[7]

Intramolecularly directed metalation through coordination with nitrogen has been demonstrated in *N,N*-dimethylbenzylamine,[8] dimethylaminomethyl- and dimethylaminoethylferrocene,[9a,b] dimethylaminomethylpyridines,[10] and arylcarboxamides.[11,12] Further, many examples of the ortho-metalation reaction with transition metal complexes having nitrogen and phosphorous donor ligands exist.[13]

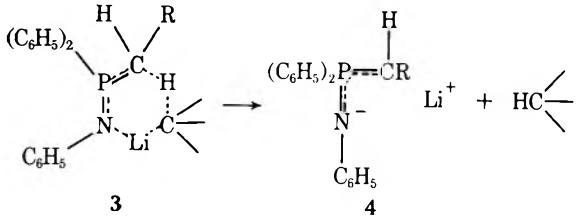


Since arylphosphine *N*-arylimides (**1**) are amenable to intramolecularly directed metalation through coordination on nitrogen and, more importantly, exhibit strong electronic effects in the rings attached to both nitrogen and phosphorous, they are interesting substrates for the study of electrophilic and nucleophilic metalations. The present paper describes our initial work pertaining to the reaction of organolithium compounds with phosphine N-arylimides.

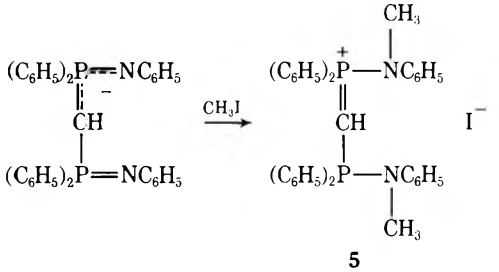
Triphenylphosphine *N*-phenylimide (**1a**) is metalated by phenyllithium to give, after carbonation, a 62% yield of 2-diphenylphosphinylbenzoic acid (**2**).



Phenyllithium metalates diphenylmethyl- and diphenyl-*n*-butylphosphine *N*-phenylimide on the carbon α to phosphorous. Lateral metalation is preferred to ring metalation because the incipient carbanion in the transition state (**3**) is resonance stabilized and collapses to the similarly stabilized carbanion (**4**).[14]

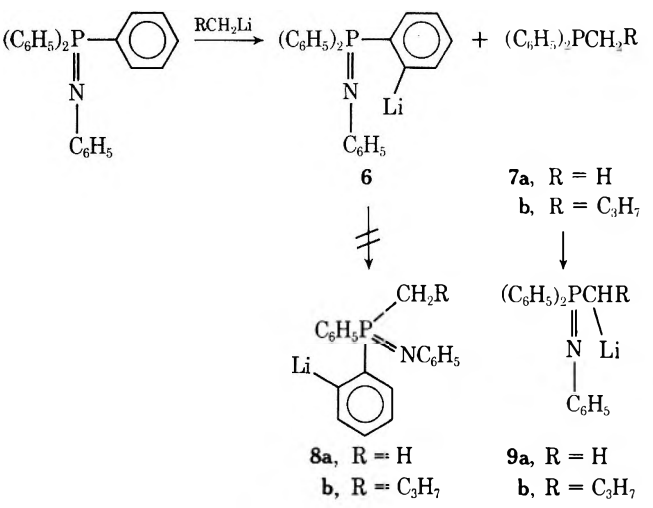


Evidence for the existence of a stabilized anion similar to **4** is presented by Kovtun et al.[15] who treated the lithium derivative of methylenebisdiphenylphosphine *N*-phenylimide with excess methyl iodide and obtained the N,N-dimethylated product (**5**). Alkylation at nitrogen rather



than carbon may be due to steric factors. An analogous situation exists for $[(C_6H_5)_2]_2CHLi$, which undergoes P-alkylations only.[16]

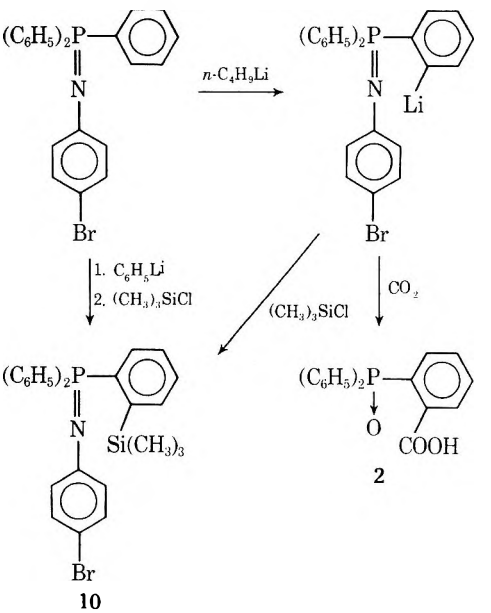
Triphenylphosphine *N*-phenylimide reacted with methyllithium to produce, subsequent to carbonation, 10% of 2-diphenylphosphinylbenzoic acid and a mixture of acids derived from a metalation-exchange sequence (**6–8a**) and/or the reverse (**7a–9a**). Conversion of **6** to **8a** was ruled out because chromatographic analysis of the mixture of carboxylic acids derived from the lithiated compounds showed the presence of derivatives of **6** and **9a** only (see Experimental Section). Furthermore, **6** was isolated from the reaction of phenyllithium with the parent ylide and then treated in separate reactions with methyl- and *n*-butyllithium, respectively. Mild hydrolysis of the reaction mixtures gave a quantitative recovery of triphenylphosphine *N*-phenylimide. The reason for the relative unreactivity of **6** may be its insolubility in the reaction medium.



With *n*-butyllithium the exchange reaction is much less pronounced. The primary metalation product amounted to 40%, and was accompanied by a very small yield (less than 5%) of the exchange–metalation product (**9b**). These results are in contrast to the metalation of triphenylphosphine oxide with alkyllithium compounds, in which exchange followed by metalation was the only observed sequence.[6] We are proposing the two-step reaction by analogy to the triphenylphosphine oxide work[6] and because tetraphenyllead was isolated after triphenyllead chloride was added to the reaction mixture between triphenylphosphine *N*-phenylimide and *n*-butyllithium, thus proving the intermediacy of phenyllithium.

Halogen–metal interchange does not compete with metalation in the reaction of triphenylphosphine *N*-(4-bromophenyl)imide with *n*-butyllithium at 0 °C. When the reaction mixture was treated with trimethylsilyl chloride the only product to be isolated was diphenyl-2-trimethylsilylphenylphosphine *N*-(4-bromophenyl)imide (**10**). Acid hydrolysis of the residual reaction mixture yielded enough *p*-bromoaniline to show that very little, if any, bromine was displaced from the phenyl ring. This was not unexpected in view of the high electron density in the *N*-aryl ring of the imide (**1**). The structure of the silylphosphine imide was proved by the transformations shown in Scheme I.

Scheme I



Experimental Section

Preparation of Phosphine Imides. Phosphine imides were prepared according to the method of Horner and Oediger.[17]

(a) Triphenylphosphine *N*-phenylimide: yield 62%; mp 125–126 °C.

(b) Triphenylphosphine *N*-(*p*-bromophenyl)imide: yield 58%; mp 126–127 °C.[18]

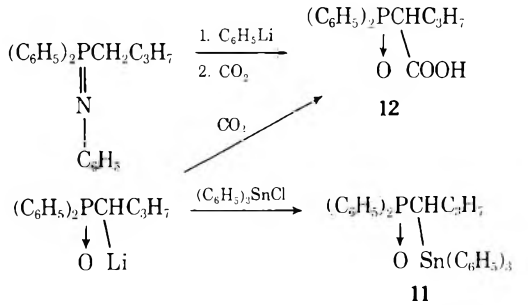
(c) Diphenylmethylphosphine *N*-phenylimide: yield 29%; mp 100–101 °C (crystallized from heptane). Anal. Calcd for $C_{19}H_{18}NP$: C, 78.4; H, 6.18; 4.77. Found: C, 78.36; H, 6.29; N, 4.67.

(d) *n*-Butyldiphenylphosphine *N*-phenylimide: yield 27%; mp 92–93.5 °C (crystallized from cyclohexane). Anal. Calcd for $C_{22}H_{24}NP$: C, 79.28; H, 7.21; N, 4.21. Found: C, 79.50; H, 7.10; N, 4.35.

Metalation of Triphenylphosphine *N*-Phenylimide with Phenyllithium. To 3.5 g (0.01 mol) of triphenylphosphine *N*-phenylimide suspended in 50 ml of ether was added 6 ml of phenyllithium (2.3 M in benzene–ether). The mixture was stirred at room temperature. The imide dissolved immediately and after 5 min a yellow precipitate formed. After 3 h the mixture was poured on pulverized dry ice suspended in dry ether. After the CO_2 had evaporated, the mixture was hydrolyzed with water, the phases were separated, and the aqueous phase was acidified with dilute HCl. The precipitated acid was collected on a filter, dried, and crystallized from 95% ethanol, yield 2.0 g (62%), mp 263–268 °C. A second crystallization raised the melting point to 266–268 °C. Schindlbauer[19] prepared 2-diphenylphosphinylbenzoic acid by oxidation of diphenyl-o-tolylphosphine with $KMnO_4$ in aqueous pyridine and reported a melting point of 242–249 °C. In a similar preparation we obtained an acid melting at 266–268 °C after several crystallizations from ethanol. The neutral equivalent and NMR spectrum were consistent with the structure assigned by Schindlbauer. A mixture melting point with the metalation product was undepressed. The ether layer from the hydrolysis of the carbonated mixture was evaporated, and the semisolid residue was triturated with ethanol. The residue, crystallized from ethanol, melted at 234–236 °C. The mixture melting point with diphenylurea was 235–236 °C.

Metalation of Diphenylmethylphosphine *N*-Phenylimide with Phenyllithium. To 1.5 g (5.0 mmol) of phosphine imide in 25 ml of ether was added 3 ml of phenyllithium in benzene–ether (2.3 M). After 3 h at room temperature the mixture was poured on dry ice–ether. After hydrolysis the aqueous layer was acidified with dilute HCl and the oily precipitate extracted with chloroform. The solution was dried over anhydrous sodium sulfate and placed on a silica gel column. The column was eluted successively with chloroform and chloroform–methanol (15:5 v/v). The first component (0.2 g) to be eluted was diphenylmethylphosphine oxide, mp 111–113 °C. The second component, after crystallization from dilute ethanol, melted at 143–145 °C. The yield was 0.65 g (52%). A mixture with diphenylphosphinylacetic acid[5b] melted at 143–145 °C.

Metalation of *n*-Butyldiphenylphosphine *N*-Phenylimide with Phenyllithium. To 1.4 g (4.2 mmol) of phosphine imide was added 3 ml of a 2 M solution of phenyllithium in ether. After 3 h at room temperature, the mixture was treated in the usual manner to yield, after crystallization from dilute ethanol, 1.0 g (83%) of an acid melting at 121–123°. Anal. Calcd for $C_{17}H_{19}O_3P$: C, 67.55; H, 6.29. Found. C, 67.40; H, 6.19. NMR 2.5 (m, 10 H), 6.4 (m, 1 H), 8.5 (m, 4 H), 9.5 (m, 3 H), −1.6 ppm (s, 1 H). A mixture melting point with 2-diphenylphosphinylpentanoic acid, prepared by metalation of *n*-butyldiphenylphosphine oxide (see below), was undepressed.



The structure of 2-diphenylphosphinylpentanoic acid (**12**) was established by its NMR spectrum, elemental analysis, and by indirect comparison with the known 1-diphenylphosphinyl-1-triphenylstannylbutane (**11**).[6b]

Preparation of 2-Diphenylphosphinylpentanoic Acid (12). To 0.025 mol of phenyllithium in 50 ml of ether was added 5.16 g (0.02 mol) of *n*-butyldiphenylphosphine oxide. After 1 h at room temperature one-half of the mixture was poured on a suspension of pulverized, solid CO_2 in ether and the other half was added to 4.8 g (0.01 mol) of triphenyltin chloride in 15 ml of ether. The carbonated mixture was processed in the usual manner and the acidic product after crystallization from dilute ethanol melted at 121–123 °C (yield 75%).

The organotin solution was treated with 25 ml of H_2O, the ether layer was separated, and the ether was evaporated. Crystallization of the residue from ether gave 4.0 g (70%) of 1-diphenylphosphinyl-1-triphenylstannylbutane (**11**), mp 148–150 °C.[6b]

Metalation of Triphenylphosphine *N*-Phenylimide with Methyllithium. Metalation of 3.5 g (0.01 mol) of imide was carried out as described above for phenyllithium. The acidified aqueous layer from the carbonation was extracted with four 10-ml portions of chloroform. The chloroform was evaporated and the crude, sticky product, 2.3 g, was crystallized from aqueous ethanol, then from acetic acid, and finally from ethanol. The yield of 2-diphenylphosphinylbenzoic acid was 0.24 g (10%), mp 265–267 °C.

The filtrate from the first crystallization was evaporated in a rotary still, and yielded after purification via the sodium salt[5b] and several crystallizations from dilute ethanol, diphenylphosphinylacetic acid, melting at 143–144 °C.

When the crude mixture of acids was converted to the methyl esters with ethereal diazomethane and then subjected to gas chromatography[20] the results showed a 12% yield of **6** and 44% of **9a**.

Metalation of Triphenylphosphine *N*-Phenylimide with *n*-Butyllithium. The reaction was carried out as described for the metalation with methyllithium and yielded 1.3 g (40%) of 2-diphenylphosphinylbenzoic acid and less than 5% of 2-diphenylphosphinylpentanoic acid. Gas chromatography[20] of the methyl esters gave 45% of **6** and 5% of **9b**.

Attempted Exchange Reaction between o-Lithiophenyldiphenylphosphine *N*-Phenylimide (6) and *n*-Butyllithium. To a suspension of 5.2 g (0.015 mol) of triphenylphosphine *N*-phenylimide (**1a**) in 50 ml of ether was added 7 ml of 2.2 M phenyllithium in benzene–ether and the mixture was stirred for 3 h at room temperature. The yellow, crystalline lithio compound (**6**) was collected on a filter in a dry N_2 atmosphere. The filtrate was hydrolyzed with H_2O and 1.2 g (0.0034 mol) of starting imide (**1a**) was recovered from the organic layer.

The lithio derivative (**6**) (identity had been established previously by conversion to the corresponding acid) was suspended in 50 ml of ether and, after addition of 7 ml of 2 M *n*-butyllithium in hexane, was stirred for 3 h at room temperature. The mixture was hydrolyzed with H_2O, 25 ml of benzene was added, and the organic layer was separated, dried over Na_2SO_4, and evaporated. The yield of recovered imide (**1a**) was 3.79 g (0.011 mol), giving a total of 0.0144 mol (96%) of recovered imide. A blank run in which *n*-butyllithium was omitted gave a 95% recovery of imide; thus no appreciable exchange took place between **6** and *n*-butyllithium.

Methyllithium. In an identical experiment methyllithium was stirred with a suspension of the lithio derivative (**6**). Ninety-four percent of the starting imide (**1a**) was recovered.

Trapping of Phenyllithium with Triphenyllead Chloride. To 0.02 mol of *n*-butyllithium in 50 ml of ether was added 3.53 g (0.1 mol) of triphenylphosphine *N*-phenylimide. After 3 h 7.1 g (0.015 mol) of triphenyllead chloride was added. The mixture was refluxed for 1 h, hydrolyzed with water, and filtered. The residue was crystallized from benzene, giving 2.5 g (48%) of tetraphenyllead, mp 228 °C.

Diphenyl-2-trimethylsilylphenylphosphine *N*-(4-Bromophenyl)imide (10). A. To 0.034 mol of *n*-butyllithium in 80 ml of ether was added 14.7 g (0.034 mol) of triphenylphosphine *N*-(4-bromophenyl)imide in 175 ml of ether at 0 °C. After the mixture was stirred for 1 h at 0 °C, 3.67 g (0.034 mol) of trimethylsilyl chloride was added. The cooling bath was removed and the mixture was refluxed for 2 h. Water was added and the layers were separated. The ether was evaporated and the residue was stirred with 50 ml of ethanol and was refrigerated overnight. The white solid which separated was crystallized from ligroin, yielding 1 g of starting imide. The ethanol filtrate was concentrated to a viscous residue which was dissolved in 75 ml of methanol. Water was added to incipient turbidity and the mixture stored at 0 °C overnight. The mixture was then filtered and the residue crystallized from cyclohexane, giving 1.85 g (10%) of diphenyl-2-trimethylsilylphosphine *N*-(4-bromophenyl)imide. Anal. Calcd for $C_{27}H_{27}BrNPSi$: C, 64.32; H, 5.35; N, 2.77. Found: C, 64.65; H, 5.50; N; 2.66.

The residues from the above crystallizations were combined and

refluxed for 6 h with 8 ml each of concentrated HCl and ethanol. The mixture was diluted with water and extracted with ether. The aqueous layer was neutralized with sodium hydroxide and extracted with ether, and the ether evaporated. The oily residue was treated with acetic anhydride to yield 5.9 g (0.029 mol) of *p*-bromoacetanilide which, after crystallization from aqueous ethanol, melted at 165–167 °C. Thus at least 95% of the bromine in the starting imide remained intact during the reaction with *n*-butyllithium.

B. To 4.32 g (0.01 mol) of triphenylphosphine *N*-(4-bromophenyl)imide suspended in 50 ml of ether was added 10 ml of 1.8 M phenyllithium in benzene–ether. After 3 h one-half of the solution was treated with CO_2 in the usual manner, yielding 67% of 2-diphenylphosphinylbenzoic acid. The other half was treated with 0.005 mol of trimethylsilyl chloride, as described in A above, and yielded 1.25 g (50%) of diphenyl-2-trimethylsilylphosphine *N*-(4-bromophenyl)imide, identical with the product from A, thus establishing the position of the trimethylsilyl group.

Registry No.—**1a**, 2325-27-1; **2**, 2572-40-9; **6**, 57901-16-3; **10**, 57901-17-4; **11**, 57901-18-5; **12**, 57901-19-6; triphenylphosphine *N*-(*p*-bromophenyl)imide, 14987-96-3; diphenylmethylphosphine *N*-phenylimide, 57901-20-9; *n*-butyldiphenylphosphine *N*-phenylimide, 57901-21-0; phenyllithium, 591-51-5; diphenylmethylphosphine oxide, 2129-89-7; diphenylphosphinylacetic acid, 1831-63-6; *n*-butyldiphenylphosphine oxide, 4233-13-0; methyllithium, 917-54-4; *n*-butyllithium, 109-72-8; triphenyllead chloride, 1153-06-6; tetraphenyllead, 595-89-1; *p*-bromoacetanilide, 103-88-8.

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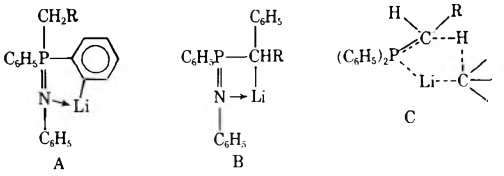

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(20) A 6 ft × 3 mm column of 3% SP2100 on 100/120 Supelcon AW-DMCS operated at 240 °C with nitrogen carrier gas (40 ml/min) was used.

Reactions of Carboxylic Acids with Organolithium Compounds

Robert Levine* and Marvin J. Karten

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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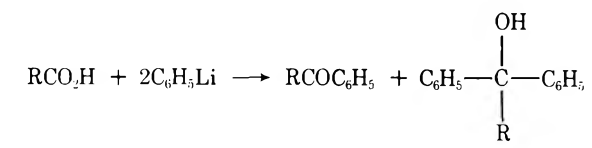
A series of carboxylic acids, RCO_2H, has been treated with a series of organolithium compounds, R'Li, to give, in most cases, a mixture of ketones, RCOR', and carbinols, $R'_2C(OH)R$. A scheme is presented to account for the formation of these products and evidence in its support is given.

Recently we reported[1] that the interaction of equivalents of lithium carboxylates and organolithium compounds for a 24-h period gave mixtures of ketones and carbinols. It was anticipated that similar results would arise from the interactions of carboxylic acids (1 equiv) and organolithium compounds (2 equiv);[2] however, quite different results were obtained (vide infra).

In the present study a series of aliphatic acids (1 equiv) and one aromatic acid (1 equiv) were allowed to react with phenyllithium (2 equiv) for 0.5 h. In all cases mixtures of ketones and carbinols were obtained.



It was thought that refluxing the carboxylic acids with phenyllithium for periods greater than 0.5 h might lead to only ketonic products as was found[1] in the reactions of preformed lithium carboxylates with phenyllithium. However, refluxing *n*-butyric acid or benzoic acid (1 equiv) with phenyllithium (2 equiv) for varying periods of time gave essentially the same yields of ketone and tertiary alcohol (Table I).

Table I. Reactions of *n*-Butyric and Benzoic Acids with Phenyllithium

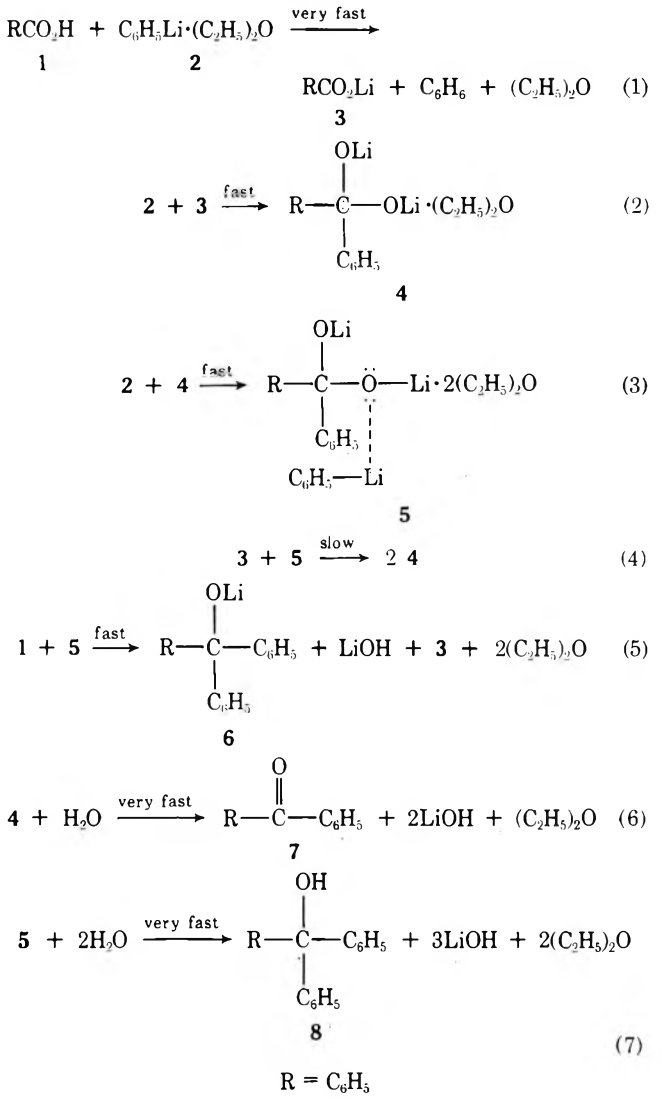
		Products, % yield	
RCO_2H, R	Reflux time, h	C_6H_5COR[a]	$(C_6H_5)_2C(OH)R$[b]
n-C_3H_7	0.5	57	25
n-C_3H_7	24	60	29
C_6H_5	0.5	54	25
C_6H_5	24	66	25
C_6H_5	96	63	25

[a] Physical constants agree with literature values [C. R. Hauser, W. J. Humphlett, and M. J. Weiss, *J. Am. Chem. Soc.*, **70**, 426 (1948)]; in each case the carboxylic acid (1 equiv) was added to phenyllithium (1 equiv). [b] Physical constants agree with literature values [H. Masson, *C. R. Acad. Sci.*, **135**, 534 (1902)].

Several other aliphatic, aromatic, and heterocyclic acids were treated with phenyllithium to give mixtures of ketones and carbinols (Table II). In addition, the reactions of benzoic acid with six aliphatic organolithium compounds

gave, in most cases, mixtures of ketones and carbinols (Table III).

The following scheme is proposed to explain the observed results, using the reaction of benzoic acid with phenyllithium as an example.



In this scheme, it is suggested (eq 1) that phenyllithium (2) reacts very rapidly, *but incompletely*, with benzoic acid (1) to give 3. Then (eq 2) 2 reacts with 3 by carbonyl addition to give 4. An adduct whose composition agrees with 4 has been isolated in the present study. It was further found that when 2 (2 equiv) is added all at once to 4 (1 equiv) in ether and the mixture is refluxed for 66 h, there is obtained almost equivalent amounts of ketone 7 (52%) and carbinol 8 (48%); this experiment indicates that 4 is unstable in the presence of 2. It might be argued that compound 4 loses lithium oxide to give the ketone, benzophenone, which then reacts to some extent with phenyllithium to give triphenylcarbinol. However, this argument appears to be untenable since the interaction of equivalents of lithium benzoate (3) and phenyllithium (2) for 24 h[1] gives only benzophenone (85%). Subsequently, 2 and 4 (eq 3) might react to give complex 5 which could participate in three reactions (eq 4, 5, and 7) to give the ketone and the carbinol or their precursors. Hydrolysis of 4 gives the ketone 7 (eq 6).

Equation 5 indicates that at some time during the reaction of phenyllithium (2 equiv) with benzoic acid (1 equiv), the acid 1 reacts with 5 in preference to reacting with 2. If this argument is valid, then treating 1 with a large quantity of 2 [so that there is always present much more phenyllithium (2) than 5] should prevent the reaction shown by eq 5 from taking place. If 3 is added at this point it should react with 5 (eq 4) to give essentially the ketone precursor, 4, and little or no tertiary alcohol should be formed. Thus, benzoic acid (1 equiv) was treated with phenyllithium (4 equiv) and the reaction mixture was refluxed for 0.5 h. Hydrolysis of an identical reaction mixture gave benzophenone (57.7%) and triphenylcarbinol (43%). Before hydrolysis, then, there should be present 58% of 4 and 43% of 5, the precursor of 6. Lithium benzoate (3, 2 equiv) was added at this point and the mixture was refluxed for an additional 24 h. Processing gave benzophenone (7, 81%), triphenylcarbinol (8, 8%), and recovered benzoic acid (1, 9%). Therefore, the results of this experiment suggest that when there is sufficient 2 present, the carboxylic acid 1 reacts preferentially with 2 rather than with 5. Subsequently, any 5 which is present is able to react with any available 3 to give 4, the precursor of the ketone.

When this last reaction was repeated except that the molar ratio of compounds 1:3:2 was 1:1:2 there was obtained benzophenone (7, 63%) and triphenylcarbinol (8, 24%). These results suggest that unless there is present a sufficiently large excess of 2 to convert most of 1 to 3, the acid 1 will react to an appreciable extent with 5 (eq 5), resulting in the formation of appreciable amounts of 6.

Table II. Reactions of Carboxylic Acids with Phenyllithium

Registry no.	RCO_2H,[a] R	Reflux time, h	Products, % yield[b] C_6H_5COR	Products, % yield[b] $(C_6H_5)_2C(OH)R$
64-19-7	CH_3	0.5	50	30
79-09-4	C_2H_5	0.5	60	28
107-92-6	n-C_3H_7	0.5	57	23
79-31-2	i-C_3H_7	0.5	58	28
75-98-9	$(CH_3)_3C$	0.5	65	26
142-62-1	n-C_5H_{11}	0.5	58	30
88-09-5	$(C_2H_5)_2CH$	0.5	49	22
65-85-0	C_6H_5	0.5	54	25
	C_6H_5	24	66	25
100-09-4	p-$CH_3OC_6H_4$	24	73	13
480-63-7	2,4,6-Trimethylphenyl	24	13	0
88-14-2	2-Furyl	2.5	47	5
527-72-0	2-Thienyl	2.5	32	10
98-98-6	2-Pyridyl	24	13	31

[a] In each case a 2:1 molar ratio of phenyllithium to carboxylic acid was used. [b] The physical constants of all the products agree with those reported in the literature.

Table III. Reactions of Benzoic Acid with Various Organolithium Compounds

Registry no.	RLi,[a] R	Products, % yield[b] C_6H_5COR	Products, % yield[b] $R_2C(OH)C_6H_5$
917-54-4	CH_3	64	0
811-49-4	C_2H_5	43	0
2417-93-8	n-C_3H_7	54	28
109-72-8	n-C_4H_9	56	23
3525-31-3	n-C_5H_{11}	54	25
21369-64-2	n-C_6H_{13}	58	32
	C_6H_5	54	25

[a] In each case a 2:1 molar ratio of RLi to $C_6H_5CO_2H$ was used and the reflux time was 0.5 h. [b] The physical constants of all the products agree with those reported in the literature.

Experimental Section

General Procedure for the Reactions Involving the Addition of Carboxylic Acids to Organolithium Compounds in Re-

fluxing Ether. A solution of carboxylic acid in 75 ml of anhydrous ether is added to the ether solution of the organolithium compound at such a rate that the ether refluxes gently throughout the addition (usually requires about 2 h). The reaction mixture is subsequently refluxed for 0.5 h, unless indicated otherwise, and then is quenched by pouring onto crushed ice and water. The phases are separated and the aqueous phase is extracted with several portions of ether. The combined basic, ether phases are dried over Drierite, the solvent and low boilers are removed at atmospheric pressure, and the residue is fractionated under vacuum. The aqueous phase is acidified with concentrated hydrochloric acid and extracted with several portions of ether. The combined acidic, ether phases are processed in the same manner as the basic ether phases.

Reaction of Diethylacetic Acid (1 Equiv) with Phenyllithium (2 Equiv). From 1.2 mol (8.3 g) of lithium, 0.6 mol (94.2 g) of bromobenzene, and 0.3 mol (34.9 g) of diethylacetic acid, there was obtained 25.7 g (48.7%) of α,α-diethylacetophenone, bp 83–85 °C (1.4 mm),[3] oxime mp 89.4–90.0 °C,[3] which showed no depression when mixed with an authentic sample, and 11.1 g (21.8%) of 1,1-diphenyl-2-ethyl-1-butanol, bp 146–148 °C (1.4 mm).[4] The carbinol was dehydrated to the olefin 1,1-diphenyl-2-ethyl-1-butene, by refluxing 11 g of the carbinol with 15 ml of acetic anhydride and 20 ml of glacial acetic acid for 2 h.[5] The olefin was then oxidized by treatment with chromic acid in glacial acetic acid[5] to a mixture of diethyl ketone (2,4-dinitrophenylhydrazone, mp 155.6–156.2 °C,[6] alone and when mixed with an authentic sample) and benzophenone (2,4-dinitrophenylhydrazone, mp 241.5–242.0 °C,[7] alone and when mixed with an authentic sample).

Reaction of Benzoic Acid (1 Equiv) with *n*-Butyllithium (2 Equiv). From 0.36 mol of *n*-butyllithium and 0.18 mol (22.0 g) of benzoic acid, there was obtained 16.5 g (56.4%) of *n*-valerophenone and 6.0 g (22.8%) of di-*n*-butylphenylcarbinol. In addition, 5.5 g (25.0%) of benzoic acid was recovered.

The yields of *n*-valerophenone and di-*n*-butylphenylcarbinol were determined by the hydroxylamine hydrochloride titration method.[8] The lowest boiling fraction, *n*-valerophenone, bp 84–88 °C (1.2 mm),[9] gave a 2,4-dinitrophenylhydrazone, mp 164.0–164.6 °C,[10] alone and when mixed with an authentic sample.

The highest boiling fraction, di-*n*-butylphenylcarbinol, bp 111–112 °C (1.2 mm),[11] was dehydrated to the olefin 1-butyl-1-phenyl-1-pentene by refluxing the carbinol with acetic anhydride and glacial acetic acid for 2 h. The olefin was extracted with ether and subsequently oxidized with chromic acid in glacial acetic acid[5] to *n*-butyric acid (*n*-butyramide, mp 114.0–114.6 °C,[12] alone and when mixed with an authentic sample) and *n*-valerophenone (2,4-dinitrophenylhydrazone, mp 164.1–164.6 °C).[10]

Isolation of the Intermediate from the Reaction of Lithium Benzoate (1 Equiv) with Phenyllithium (1 Equiv) in Refluxing Ether. Lithium benzoate was added to phenyllithium and the reaction mixture was refluxed for 96 h. The ether was removed by filtration through a filter stick. The precipitate which remained was washed with three 200-ml portions of dry ether and the solvent was removed by use of the filter stick. The residual solid was dried at 20 mm pressure for 2 h at room temperature. From 0.3 mol (2.1 g) of lithium, 0.15 mol (23.6 g) of bromobenzene, and 0.15 mol (19.2 g) of lithium benzoate, there was obtained 41.2 g (96.3% yield) of a solid. The yield is based on the assumption that the solid is a monoetherated adduct of lithium benzoate and phenyllithium. Three samples of this solid were weighed and titrated with standard hydrochloric acid to give experimental equivalent weights of 143.0, 144.8, and 147.0. The calculated equivalent weight of a monoetherated adduct of lithium benzoate and phenyllithium is 142.9. A 5.0-g sample of this solid, upon hydrolysis, gave 2.8 g (90.0%) of benzophenone, mp 50.1–51.0 °C alone and when mixed with an authentic sample.

Reaction of Benzoic Acid (1 Equiv), Lithium Benzoate (2 Equiv), and Phenyllithium (4 Equiv). One equivalent of benzoic acid was added to 4 equiv of phenyllithium and the reaction mixture was refluxed for 0.5 h. Two equivalents of lithium benzoate was then added to the reaction mixture and the mixture was refluxed for 24 h. From 0.8 mol (5.6 g) of lithium, 0.4 mol (62.8 g) of bromobenzene, 0.1 mol (12.2 g) of benzoic acid, and 0.2 mol (25.6 g) of lithium benzoate, there was obtained 44.0 g (80.6%) of benzophenone, mp 50.1–51.0 °C, and 2.0 g (7.8%) of triphenylcarbinol, mp 159.5–159.9 °C.[13] In addition, 8.2 g (8.7%) of benzoic acid was recovered.

Reaction of Benzoic Acid (1 Equiv) with Phenyllithium (4 Equiv). From 0.8 mol (5.6 g) of lithium, 0.4 mol (62.8 g) of bromobenzene, and 0.1 mol (12.2 g) of benzoic acid, there was obtained 10.5 g (57.7%) of benzophenone, mp 50.1–51.0 °C, and 11.2 g (43.1%) of triphenylcarbinol, mp 159.6–160.0 °C.[13]

Registry No.—Lithium benzoate, 553-54-8; phenyllithium, 591-51-5.

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Interaction of α-Pinene with Carboxylic Acids

G. N. Valkanas

Technical University of Athens, Laboratory of Organic Chemical Technology, Athens, Greece

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The interaction of α-*d*-pinene with a series of organic acids from acetic to octanoic, under a wide range of olefin to acid ratios, yields esteric and rearrangement products after ring opening to the *p*-menthane system and ring rearrangement to the camphane system. Evidence is presented that the esterification proceeds through two distinct mechanisms one of which is highly dependent on the ionizing power and the nucleophilicity of the solution. This reaction leads to α-terpinyl esters while the esterification to bornyl and α-fenchyl esters is a reaction of zero order in the organic acid that constitutes 23.6 ± 1.5% of total product under all conditions. Furthermore, the bicyclic esters bornyl and α-fenchyl are produced in a constant ratio (bornyl/α-fenchyl = 1.6 ± 0.2). The esterification to give the terpinyl esters is explained as proceeding through solvolysis of a carbonium ion after a ring bond rupture. The esterification to give bornyl and α-fenchyl esters is considered to be the result of the filling of the vacant orbital created after a skeletal rearrangement with strain release from the pinane to the camphane skeletal system. The isomerization reaction is also suggested as following two reaction paths, one through carbonium ion intermediates producing limonene and terpinolene and the other through nonclassical intermediates with distributed charge to produce camphene and α- and β-fenchenes. For all these reactions consistent mechanistic explanations of the results are given.

Whereas the reaction of α-pinene with organic acids has received wide attention, the nature and the course of these reactions is still poorly understood. α-Pinene reportedly reacts with organic acids to yield bornyl esters and isomerization products.[1] The number of products was later enlarged to include α-fenchyl and α-terpinyl esters and the isomerization products limonene, terpinolene, and campene.[2] These findings were used by Meyer to test his stereochemical hindrance theory.[3] The reaction was interpreted in terms of the strength of the organic acid and the amount of bornyl ester formed,[4] but other workers found this to be inconsistent.[5] According to a more recent work, the reaction of α-pinene with the lower organic acids leads mainly to α-terpinyl esters, while the higher carboxylic acids produce mainly bornyl.[6]

In a preliminary publication on the reaction of α-pinene with acetic acid,[7] results were presented which show some special features of interest. The esterification reaction was found to be very sensitive to the excess of acetic acid both in the amount and kind of products. The esterification proved to be of solvolytic character with respect to α-terpinyl acetate while the formation of bornyl and α-fenchyl acetate showed an indifference to the ionizing power of the solvent. These observations were not in line with previous reports and it was thought to be desirable to further investigate the system with respect to changes in the ionizing power and the nucleophilicity of the reaction media for mixtures of α-pinene and straight-chain fatty acids from acetic to octanoic. Such information seemed useful in order to better understand the complex chemistry of terpenes, among which α-pinene has a key position and is of considerable industrial importance.

Results

The acetolysis of α-pinene was followed both kinetically and by product analysis, mainly at 150 °C over a wide range of dilution. The acetolysis, because of its key importance, was also followed at 105 °C. The methods employed for the kinetic study and the analysis of the reaction products are described in the Experimental Section.

The calculated first-order solvolysis constants at 150 °C at a dilution of organic acid to α-*d*-pinene of 4:5 (M/M), drop rapidly from acetic to butyric acid, then remain constant (Table I). This shows that from butyric acid and higher, the organic acids show a form of reactivity toward α-*d*-pinene that is independent of their molecular weight and the differences in mobility it creates. Such behavior

Table I. Solvolysis Rate Constants of α-Pinene Giving Simple First-Order Kinetics in Organic Acid Solutions at 150°C[c]

Acid	$k \times 10^4$, min	k in acetic acid / k in other acids A[a]	B[b]
Acetic	120	1	1
Propionic	42	2.38	1.19
Butyric	8.9	13.3	2.02
Pentanoic	8.55	14.0	2.02
Hexanoic	8.40	14.3	2.02
Heptanoic	8.35	14.4	2.02
Octanoic	8.28	14.5	2.02

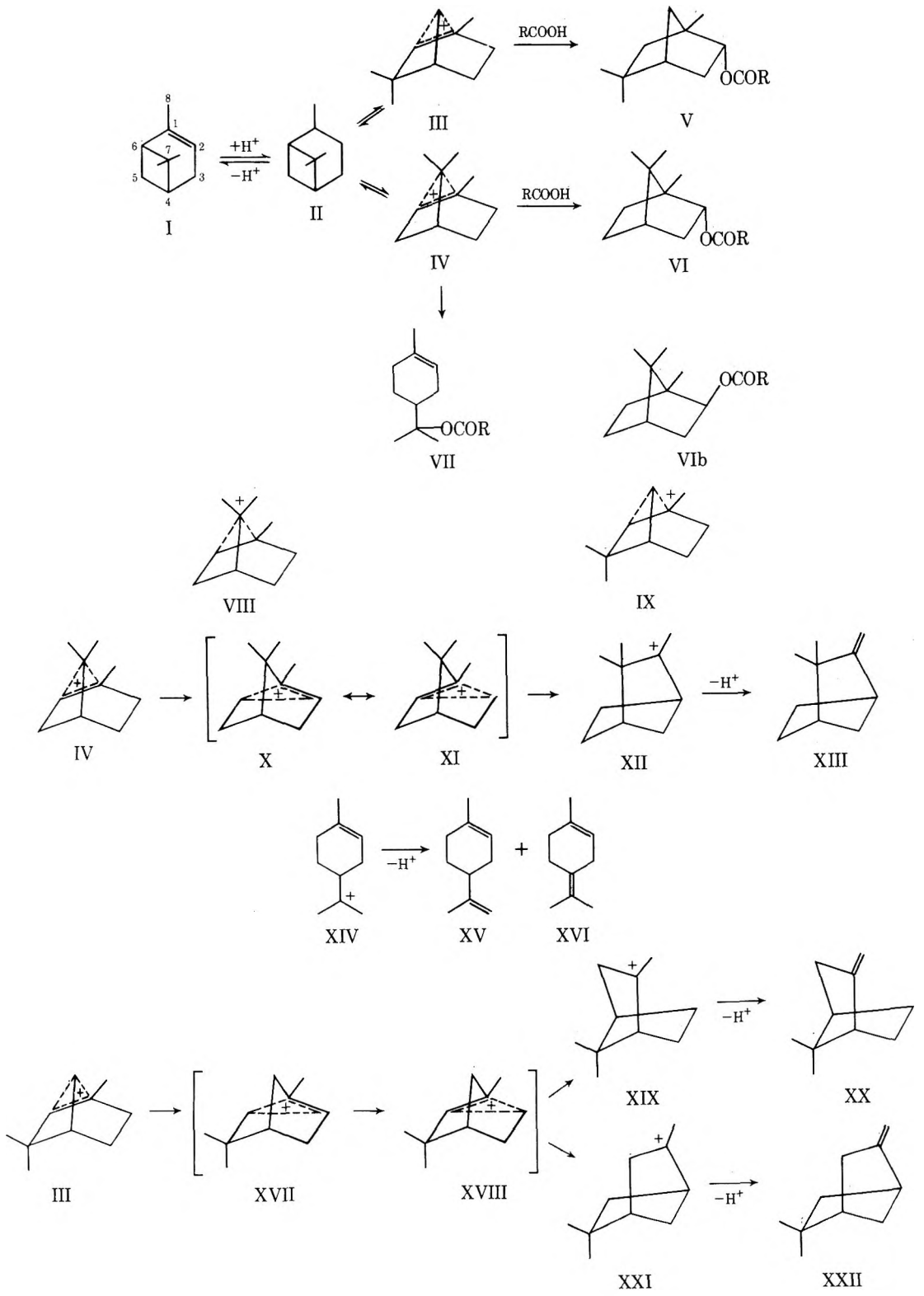
[a] In the present system. [b] In the esterification with methanol[8] at 40°C. [c] Organic acid: α-pinene, 4.5 M/M.

was first observed in the esterification of organic acids with alcohols (which has led to the Newman rule of six[8]), but has not been reported for esterifications involving ring bond rupture.

Apart from the effect on the solvolysis rates, the structure of the organic acids has a pronounced effect on the nature of the esterification products. While the lower acids acetic, propionic, and chloroacetic give mainly α-terpinyl esters in amounts corresponding to their relative ionizing power, which decreases in the series,[9] the acids from butyric to octanoic give total ester formation and esteric product composition that changes very little. This difference in esteric products for the different C_2 to C_8 acids refers to the α-terpinyl esters only; the amounts of bornyl and α-fenchyl esters remain practically unchanged for the whole series of acids.

In the Newman rule of six, the lower equal to al., reactivity of butyric acid and higher[8] is explained in terms of steric repulsion between the carboxylic group and the hydrogens of the sixth position in the chain. It seems, therefore that the esterification to give terpinyl esters has a different nature than the formation of bornyl and α-fenchyl esters. In the first case unhindered carboxylic groups are particularly effective while in the second the nature of the carboxylic group makes no difference.

In Table II are summarized the results for the esterification reaction using identical acid dilutions. The amount of esterification is shown to decrease from 50 to 28% between acetic acid and butyric acid and by 4% between butyric and octanoic acid. These changes in ester formation are due to



the terpinyl ester produced; the amounts of bornyl and α-fenchyl ester do not change significantly along the series.

Also characteristic is the picture given by the composition of the isomerization products (Table III). As the isomerization reaction becomes more important with the change from C_2 to C_8 acids, the isomerization products become richer in camphene (from 10% of overall reaction product with C_2 to 29% in the case of octanoic acid). Limonene, the other major isomerization product, also increases substantially from acetic acid to butyric acid and then slowly decreases. Terpinolene, which in the acid-catalyzed hydration of α-pinene in 70% aqueous acetone constitutes the major isomerization product,[10] makes only a small 5–7.5% contribution to the overall products.

The results of Tables II and III conceivably show that at equal dilutions the amount of α-terpinyl ester is related to the strength of the acid. These results, however, do not give a complete picture for the reaction system. In the interaction of α-*d*-pinene with organic acids, the product composition is also highly dependent on the degree of dilution. By changing the degree of dilution in the reaction systems of α-pinene and the acids acetic, propionic, and butyric, a strong response of different degree is observed in each case. This refers to changes in the formation of α-terpinyl esters

Table II. Solvolysis Products of α-Pinene in Organic Acid Media at 150°C

Acid	Registry no.	Organic acid/α-pinene, M/M	Esterification, %	Percent ester composition[a] α-F-OCOR	B-OCOR	α-T-OCOR
Acetic	64-19-7	4.5	50.0	18.0	30.0	52.0
Propionic	79-09-4	4.5	36	25.2	42.8	32.0
Butyric	107-92-6	4.5	28	31.6	54.2	14.2
Pentanoic	109-52-4	4.5	27	32.1	56.8	11.1
Hexanoic	142-62-1	4.5	26	32.6	57.5	9.9
Heptanoic	111-14-8	4.5	24.5	33.3	58.0	8.7
Octanoic	124-07-2	4.5	24	33.6	58.5	7.9
Chloroacetic	79-11-8	4.5	35.5	25.1	43.5	31.4

[a] α-F-OCOR, α-fenchyl ester; B-OCOR, bornyl ester; α-T-OCOR, α-terpinyl ester.

Table III. Isomerization Products during Solvolysis of α-Pinene in Organic Acid Media at 150°C[a]

Acid	Isomerization %	Percent isomerization product composition Cf	Fc	Lm	Tp
Acetic	50	20.1	6.6	58.5	14.8
Propionic	64	20.2	5.5	64.8	9.5
Butyric	78	26.0	5.0	60.0	9.0
Pentanoic	73	27.7	5.5	59.0	7.8
Hexanoic	74	30.9	5.3	56.7	7.1
Heptanoic	75.5	35.0	5.1	53.4	6.5
Octanoic	76	38.8	5.0	55.0	5.2
Chloroacetic	64.5	22.0	5.0	62.8	10.2

[a] Organic acid: α-pinene, 4.5 M/M.

and camphene, because in part of formation of bornyl and α-fenchyl esters, there is no significant change created by dilution. These results are included in Table IV and clearly show that in the system of α-pinene and the organic acids, the important parameters of reactivity are the ionizing power of the reaction medium and the nucleophilicity of the reagents, and not the strength of the acids. It is further concluded that in this reaction system two distinct reaction paths operate, one of which is very sensitive to the ionizing power while the other is not.

In addition to the ionizing power, the system was tested for response toward nucleophilic reagents, by adding small amounts of water to the reaction system acetic acid–α-pinene. The results obtained (Table V) show that nucleophilicity is an important factor of reactivity since 0.2–5% of added water changes the overall reactivity with an increase of 10% in the substitution products while a share of 21.5% is being taken by the alcohols. α-Terpineol is the main hydration product formed at amounts ca. 15 times higher than borneol and ca. 27 times higher than α-fenchyl alcohol.

Discussion

The bornyl (VI) and α-fenchyl (V) esters, at the same degree of dilution, make a constant part in the transformation of α-pinene (I) to products, some 23.6 ± 1.5% total reaction under variations in the kind of acid and temperature. Furthermore, the ratio of bornyl/α-fenchyl esters re-

Table IV. Effect of Solvent Dilution on Product Composition during Solvolysis of α-Pinene in Organic Acid Media at 150°C

Acid	Organic acid/α-pinene, M/M	Esterification, %	Percent ester composition α-F-OCOR	B-OCOR	α-T-OCOR	Percent isomerization product composition[a] Cf	Fc	Lm	Tp
Acetic	0.8	34	31.2	48.0	20.8	51.01	12.7	35.5	9.6
	1.9	41.5	24.6	37.6	28.8	26	9.0	52.5	12.5
	4.5	50.0	18.0	30.0	52.0	20.1	6.6	58.5	14.8
	6.75	55.0	14.9	24.2	60.9	17.5	6.9	58.8	16.8
	11.3	59.0	13.5	20.5	66.0	15.7	5.5	61.0	17.8
Propionic	1.9	31.0	29.3	48.7	22.0	29.0	5.0	58.0	8.0
	3.0	33.0	27.4	45.3	27.3	26.0	5.0	60.4	8.6
	4.5	36.0	25.2	42.8	32.0	20.2	5.5	64.8	9.5
	6.5	38.0	23.4	40.0	36.6	19.0	5.0	66.0	10.0
	9.75	40.5	22.0	37.4	40.6	17.0	5.0	67.5	10.5
Butyric	1.4	25.0	34.6	59.6	5.8	32.5	6.1	54.3	7.1
	3.0	26.0	33.0	57.0	10.0	29.2	5.5	57.5	7.8
	4.5	28.0	31.6	54.2	14.2	26.0	5.0	60.0	9.0
	7.0	29.0	30.5	54.6	14.9	24.0	5.0	61.5	9.5
	10.0	30.0	30.6	52.7	16.7	23.0	5.0	62.0	10.0

[a] Cf, camphene; Fc, fenchenes; Lm, limonene; and Tp, terpinolene.

Table V. Acetolysis of α-Pinene in the Presence of Water at 105°C[b]

Water added, %	$k \times 10^3$, min	Substitution, %	Percent solvolysis product composition[a] F-OCOR	B-OCOR	α-T-OCOR	F-OH	B-OH	α-T-OH
0.75	3.35	60.8	14.5	23.0	56.7	0.2	0.4	5.2
2.5	3.6	64.8	11.0	16.0	57.4	0.5	0.9	14.4
5.0	3.8	67.5	8.0	12.0	58.5	0.7	1.4	19.4

[a] F-OH, α-fenchyl alcohol; B-OH; bornyl alcohol; α-T-OH, α-terpinyl alcohol. [b] α-Pinene:acetic acid 20:60 by weight.

mains constant (1.6 ± 0.1) under all conditions of reaction (Tables II and IV). These results can be interpreted in terms of two different reaction paths with intermediates like III and IV, for which the esterification reaction follows the skeletal rearrangement. Similar intermediates to III and IV in form of nonclassical carbonium ions have been proposed for the reaction of cis and trans α-pinanes.[11]

The esterification to bornyl and α-fenchyl esters is independent of the concentration of the organic acid and of the ionization power and nucleophilicity of the reaction medium. Therefore, it is not the result of substitution on an electron-deficient center, but a reaction of zero order on part of the acid, which develops by filling a gradually formed vacant orbital at C_6, during a skeletal rearrangement with strain release from the pinane to camphane skeletal system. The approach of the acid molecule to the C_6 carbon atom, according to the above, can be effective only from the endo side of the molecule through a bond making while an exo bond breaking is progressing. The suggestion can explain the fact that both bornyl and α-fenchyl esters are endo products. In no case was an exo product such as an isobornyl ester (VIb) detected.

In intermediates like III and IV the positive charge cannot be equally distributed among the carbon atoms of the electron-deficient three-carbon center, since the tertiary carbon atoms C_7 in IV and C_1 in III can better support a positive charge. To better demonstrate this, in another case, structures like XIII and IX have been proposed.[12] According to these postulated structures the intermediate IV resembles the products more than III, which is more like the starting material and more liable to return to it. Since esterification to give bornyl and α-fenchyl ester is not a single step but a transformation following the skeletal rearrangement, one can suggest that the ratio in which these esters are formed should be the measure of effective aptitude toward structural arrangements like IV or III. It follows that structure orientation to IV is favored over III by a factor of 1.6:1, which seems to be in accordance with the expected differences in stability of the two ionic intermediates.

Intermediate IV, because of its carbonium ion character at C_7, should be very susceptible to solvent attacks at that carbon center. Such a solvolysis on the top of the three-carbon center is highly favored because of charge location and because it relieves the strained bridge structure. Such a solvolysis with bond breaking will produce α-terpinyl esters (VII) and limonene (XV) and terpinolene (XVI). The ionic character of the intermediate IV is expected to strongly depend on the ionizing power of the reaction medium, while reaction to produce esters will additionally depend on the nucleophilicity of the reagents.[13] This is in accord with the observed solvolytic efficiency to produce α-terpinyl esters which decrease in the series acetic, chloroacetic, propionic acid (Table II). The ionic character of the carbonium ion intermediate IV is in agreement with the results obtained by adding water in the acetolysis reactions (Table V). The addition of 0.2–5% of water led to 21.5% of alcoholic products, 90.5% of which is α-terpineol. That also means that water has an efficiency for capturing the intermediate IV that is ca. 6.5 times higher than that of acetic acid. Water is a strong nucleophilic reagent widely used to test the carbonium character of reaction intermediates.[9] Its inability to promote formation of the bornyl and the α-fenchyl systems is in accordance with the foregoing proposal of a nonionic character for these transformations.

Other fates of the intermediate IV are either to return to α-pinene or to undergo skeletal transformation with release of strain to produce camphene (XIII). That camphene derives from an intermediate like IV can be seen from its competition with the α-terpinyl esters and the *p*-menthadienes (Tables II–IV). It decreases under conditions that promote solvolytic ring opening, such as dilution of the organic acid, and increases with the molecular weight of the organic acid. By changing the ratio of organic acid:α-pinene in acetic acid from 0.8 to 11.3 (M/M), in propionic acid from 1.9 to 9.75 (M/M), and in butyric acid from 1.4 to 10 (M/M) the amount of camphene in the overall reaction decreases from 28 to 6.4% (acetic), 20 to 10.3% (propionic), and 24.1 to 16.5% (butyric). The change in the molecular weight from acetic to octanoic at equal dilutions increases the amount of camphene formed from 10 to 28.8% (Table II). These results suggest that the formation of camphene, which results in strain release, proceeds through intermediates that do not involve heterolytic bond breaking. These changes can be formulated as in X–XI.

The camphene obtained from the isomerization of α-pinene is racemic in support of the suggestion that it is formed through symmetric intermediates like X–XI.[14]

The intermediate III also shows structural similarities with the reaction products α- and β-fenchene. These make up 2.5–8.3% of the reaction and their formation varies along with the α-fenchyl ester formation (Table IV). The reaction leading to α- and β-fenchene can be better formulated with the mechanistic scheme XVII–XVIII.

The intermediate XVII is not symmetric like the corresponding one proposed for camphene formation, and a structure assignment more consistent with the results is to have two resonating forms. These forms develop further along the two possible reaction paths leading either to α- (XXII) or to β-fenchene (XX).

Ions such as X–XI and XVII–XVIII have been proposed in a number of cases to explain reactivities in the camphanyl and norbonyl systems.[15] The occurrence of common intermediates between camphene and the fenchenes with the *p*-menthadienes has been demonstrated in the deamination of bornyl- and α-fenchylamines, which gave considerable ring opening.[16] From the bornyl- and α-fenchylamine deamination, the main product was α-terpineol.[17] The isobornylamine treated in the same manner gave little ring opening, which indicates special requirements for reversibility through X–XI and XVII–XVIII. These results are interpreted[17] by a series of ionic bond ruptures and bond rearrangements which are unlikely to occur and which cannot account for the deamination of the exo amines. A more consistent explanation, fitting with the present results, is a low energy reversibility of the ions X–XI and XVII–XVIII to produce the fundamental ion intermediates III–IV, which then collapse to products according to the proceedings.

By analogy the deamination of norbornylamines leads to skeletal rearrangements.[18] The deamination of the endo isomer in acetic acid gave 100% of stereospecificity for the normal but only 19% for the exo acetate and was suggested to proceed through nonclassical carbonium intermediates like X–XI and XVII–XVIII.

High-temperature isomerization of T-OH vapor has been reported to give certain amounts of camphene;[19] this, however, was later definitely reidentified as 3-menthane.[20] With this correction there is no evidence to our knowledge for the transformations from the *p*-menthane to the camphane bridged system. Evidently, the reaction of α-pinene to give camphene proceeds through intermediates with distributed charge without ionic bond rupture like XIV suggested for the isomerization to *p*-menthadienes.

According to the above suggestions and the results (Table IV), reactivity through intermediate IV is thus most favored, accounting for 80–90% of reaction products.

In a study based on product analysis rather than on a de-

tailed kinetic study, the addition of acetic acid to α-pinene in solutions 0.2 N in sulfuric acid at 20 °C is explained with an intimate ion-pair mechanism. According to this suggestion the intimate ion pair favors elimination rather than substitution the ratio of which is said to depend on the ionization constant of the acid.

The nonclassical ion intermediates III, IV, VIII, and IX suggested by us here and elsewhere[7,11] evidently are ion pairs; however, from the results and the foregoing discussion it is rather conclusive that their reactivity does not involve collapse with bonding of the counterion but rather reaction through solvolysis and substitution. Furthermore, the addition of organic acids to α-pinene does not depend on the ionization constant of the acids[5] (Table II); the acetolysis of α-pinene gives less than 10% total esters and 90% rearranged products[21] mostly not primarily involved.[7,11]

The reaction of α-pinene with the organic acids presented above shows interesting stereochemical and mechanistic features which are unique for this natural products. Further work to demonstrate the reactivity of α-pinene with its preference for formation in nature and its structural connections with the terpenic hydrocarbons in general and the steroids in particular may be useful and interesting.

Experimental Section

α-*d*-Pinene was obtained from turpentine oil of *Pinus halepensis var.* containing α-pinene (ca. 96% by weight). After 6 h of refluxing over solid KOH and distilling through an efficient column, the α-*d*-pinene was obtained in ca. 99% GLC purity: bp 154–156 °C (770 mmHg); $n^{20}D$ 1.4665; $\alpha^{20}D$ +38.86°.

Organic acids were analytical grade reagents (obtained from Fluka AG, Switzerland), further purified by distillation over chromium oxide.

Kinetics. The solvolysis rates and the product analyses were determined by sampling aliquots at appropriate time intervals, using gas chromatography as the analytical method (Perkin-Elmer Model 801), equipped with ionization detector.

Product Analysis. In a typical run, the appropriate solution of α-*d*-pinene in the organic acid was divided in five to six ampules (Pyrex glass), holding 50 ml of solution each. These were inserted into a thermostated bath and were used for the determination of the course of the reaction in reaction rates and product composition. Each ampule, when withdrawn from the kinetic bath, was cooled and poured under stirring into a cold mixture of 50 ml of purified *n*-pentane and 100 ml of 5% NaOH–water solution. The *n*-pentane layer was further washed with sodium bicarbonate and carefully concentrated.[23] This was divided into three parts, A, B, and C. Part A was used for preparative chromatography, to separate the terpene fraction, which was further analyzed on macro-Golay chromatographic columns. Part B, after complete evaporation of *n*-pentane, was used to determine the saponification number using a 3-h boiling in 90% aqueous ethanolic solution of 0.3 N KOH, under standardizing conditions. Part C was used to determine by GLC the ester composition, in the ester form (case of runs in acetic and propionic acid), or in the form of alcohols after a lithium aluminum hydride reduction.[22] For the reduction part C was diluted with ether and treated with lithium aluminum hydride, under cooling. After hydrolysis with saturated aqueous ammonium chloride, the ether layer was washed with water and dried over potassium carbonate and the ether was evaporated.[23] The residue was taken up in *n*-pentane and analyzed by GLC.

In the alcohol and terpene determinations, bromobenzene was used as internal standard. The measured peak areas of terpene–alcohols and terpene–esters mixtures were corrected for the relative detector response by 1:1.1 and 1:1.08, respectively, determined by analysis of mixtures of known composition. Dehydration of alcohols and elimination in the esters were negligible under these conditions of analysis. The concentration of each was calculated by multiplying the peak height by the half-width, with correction for relative detector response. In a careful series of control experiments it was established that synthetic mixtures could be analyzed with an average error in percent of composition of terpenes 1.5%, alcohols 0.8%, and esters 1.2%.

From runs with dilution of organic acid–α-pinene (4.5 M/M), first rate constants were calculated using the expression $k = 2.303/t \log 100/x$ where x is the percent of unreacted α-*d*-pinene at time t. The amount of unreacted α-*d*-pinene was determined from the gas chromatographic analysis of the terpene mixture, through the esterification number obtained in each measurement.

Registry No.—I, 7785-70-8.

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(23) Under a 1-m packed fractionating column.

Selective Halogen–Lithium Exchange in Bromophenylalkyl Halides[1]

William E. Parham,* Lawrence D. Jones, and Yousry A. Sayed

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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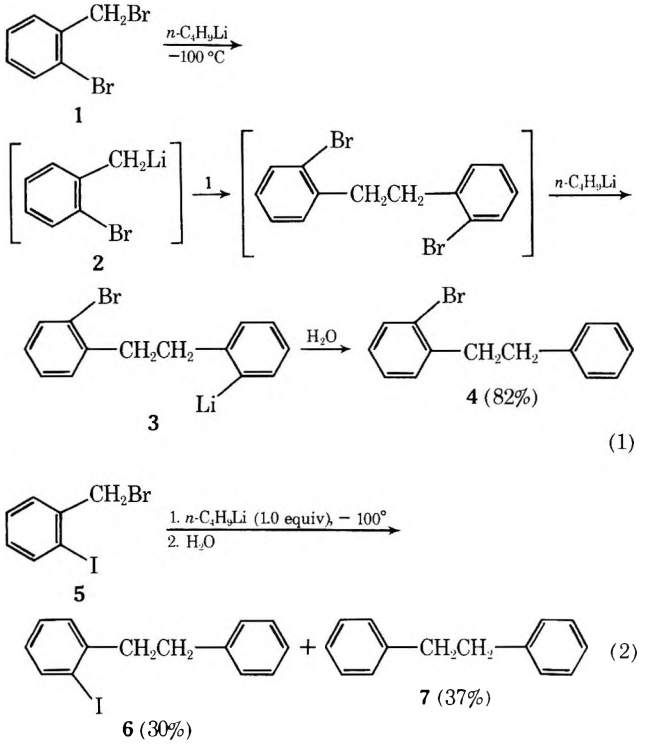
Halogen–metal exchange with a variety of bromophenylalkyl halides at low temperature (−100 °C) is selective and the order of exchange is $ArCH_2Br > ArBr > ArCH_2CH_2Br > Ar(CH_2)_nCl$. Thus, stable lithioaryl derivatives, which can be elaborated by addition of E^+, are obtained from *o*-bromobenzyl chloride, β-(*o*-bromophenyl)ethyl bromide, and γ-(*o*-bromophenyl)propyl chloride. Intramolecular cyclization occurs rapidly at −100 °C with γ-(*o*-bromophenyl)propyl bromide. Coupling occurs by primary benzylbromine–metal exchange with benzyl bromides. Attempts to prepare benzocyclopropene from o-lithiobenzyl chloride leads instead to 9,10-dihydroanthracene. A number of synthetic applications are discussed including a new, convenient synthesis of benzocyclobutene.

The success achieved for the elaboration of aryl bromides containing functional groups[2] that are normally reactive to alkyl- or aryllithium reagents by halogen–metal exchange at very low temperature (−100 °C) has prompted us to examine related reactions with aryl bromides containing haloalkyl functional groups. Complete selectivity has been observed and the order of halogen–metal exchange has been found to be $ArCH_2Br > ArBr > ArCH_2CH_2Br > Ar(CH_2)_nCl$. Halogen–metal exchange reactions were generally conducted at −100 °C in tetrahydrofuran–hexane with *n*-butyllithium. The course of reactions was followed by quenching aliquots with water and examining products both by NMR and by comparing GLC retention times with those of authentic samples, and subsequently by isolation of products.

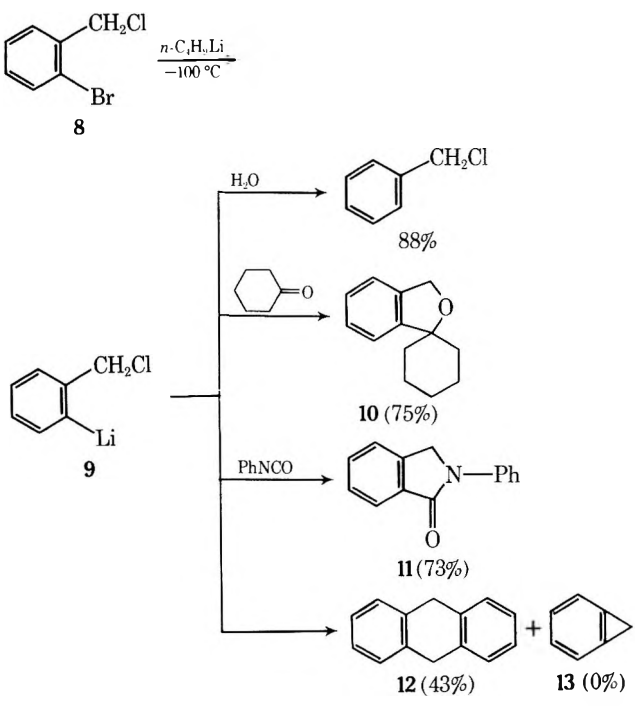
***o*-Bromobenzyl Bromide and *o*-Iodobenzyl Bromide.** Reaction of *o*-bromobenzyl bromide with 1 equiv of *n*-butyllithium gave 2-bromobibenzyl (**4**, 82% isolated yield) which is consistent with initial bromine–metal exchange at the benzyl bromide function as shown in Scheme I (eq 1).

Scheme I



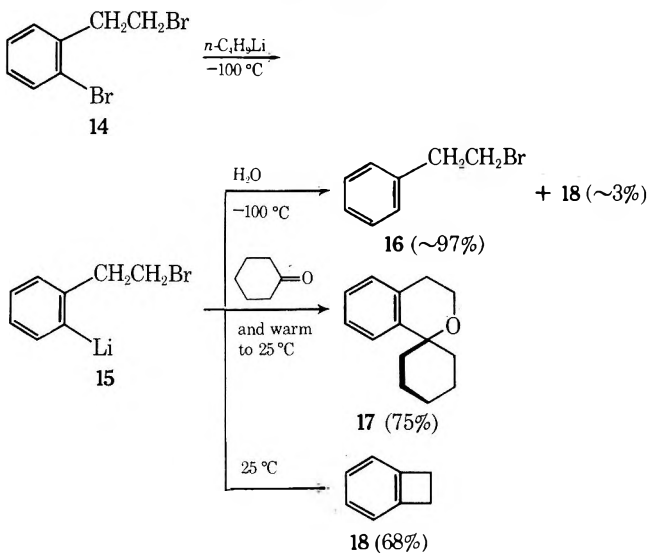
This was unexpected in view of the earlier report[3] which suggested that halogen–metal exchange occurred at the aryl halide function in a similar reaction with *p*-bromobenzyl bromide. When excess (2 equiv) of *n*-butyllithium was employed the product was bibenzyl, the product expected by complete halogen–metal exchange in **3** prior to the addition of water. Similar results were obtained with *o*-iodobenzyl iodide (**5**); however, the distribution of products (**6**, 30%; **7**, 37%) was different from that obtained with 1 when 1 equiv of *n*-butyllithium was employed.

Scheme II



***o*-Bromobenzyl Chloride (8).** Reaction of **8** follows a dramatically different course of reaction than that observed for **1**; o-lithiobenzyl chloride (**9**) is formed exclusively at −100 °C after approximately 5 min when 1 equiv of *n*-butyllithium is employed. o-Lithiobenzyl chloride is stable in solution at −100 °C and can be elaborated as shown in Scheme II: (a) by conversion to benzyl chloride (88% isolated yield) by addition of water, (b) by conversion to spiro[cyclohexane-1,1′-phthalan] (**10**, 75% isolated yield) by addition of cyclohexanone, and (c) by conversion to *N*-phenylphthalimidine (**11**, 73% isolated yield) by addition of phenyl isocyanate. Considerable effort was made to determine whether **9** might be converted to benzocyclopropene (**13**), particularly since Radlick and Crawford[4] have observed formation of benzocyclopropene by a similar process involving o-bromobenzyl methyl ether and *n*-butyllithium at −40 °C. Samples of **9** in the tetrahydrofuran–hexane solvent mixture were allowed to warm to room temperature prior to decomposition with water.[5] The product was pro-

Scheme III

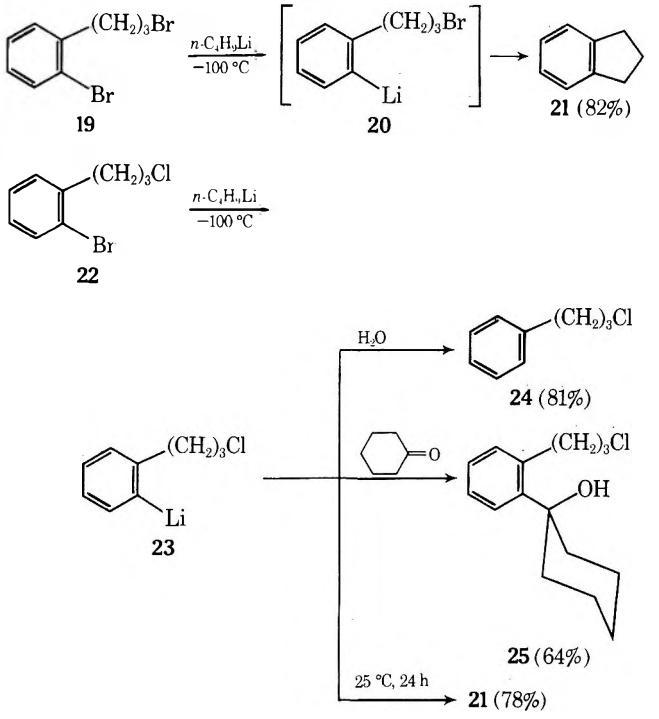


cessed at room temperature to minimize possible decomposition of **13**; however, only benzyl chloride, 9,10-dihydroanthracene (**12**, 43% isolated yield), and higher condensation products were detected. Similar results were obtained when **9** was formed in more dilute solutions of solvent.

β-(*o*-Bromophenyl)ethyl Bromide (14). Aryl halogen–metal exchange by reaction of **14** with *n*-butyllithium is selective at −100 °C; the lithio derivative **15** is formed rapidly (approximately 5 min) and can be elaborated as shown in Scheme III. The intramolecular cylization of **15**, which occurs when **15** is warmed, constitutes a new and highly efficient synthesis of benzocyclobutene[6] (**18**).

γ-(*o*-Bromophenyl)propyl Bromide (19). While one can anticipate selectivity in halogen–metal exchange similar to that described for **14** for *m*- and *p*-bromoalkyl halides, certain ortho isomers, such as **19**, present a new problem since entropy factors are favorable for intramolecular cyclization. In order to test this possibility the reactions of **19** and **22** with *n*-butyllithium at −100 °C were examined (Scheme IV). Only indan (**21**, 82% isolated yield) was detected (NMR) when **20** was formed and quenched at −100 °C with water. By contrast, γ-(*o*-lithiophenyl)propyl chloride (**23**) is formed selectively and is stable at −100 °C, and can be elaborated as shown by (a) its conversion to γ-phenylpropyl chloride (**24**, 81% isolated yield) by addition of water, and (b) by formation of **25** (64% isolated yield) by addition of cyclohexanone. When the solution containing **23** is warmed to room temperature, intramolecular cyclization occurs giving indan (**21**, 78% isolated yield).

Scheme IV



These results suggest a broad spectrum of utility in synthesis for lithioarylalkyl halides formed at low temperature from bromoarylalkyl halides.

Experimental Section

General Procedure for Halogen–Metal Exchange. Reaction of haloarylalkyl halides (0.02 mol) with *n*-butyllithium (1 molar equiv) in dry tetrahydrofuran (~130 ml)–hexane[7] (~40 ml) was carried out similar to that described for bromobenzoic acids[2a] and bromobenzonitriles.[2d] Aliquots were examined as described in ref 8.

Reaction of *o*-Bromobenzyl Bromide (1) with *n*-Butyllithium. Examination of an aliquot[8] showed complete disappearance of 1 after 30 min. The solution was stirred for a total of 1 h at −100 °C and was poured into dilute hydrochloric acid (~100 ml). The organic product, obtained from the dried ($MgSO_2$) ether extract, was essentially pure (GLC) 2-bromobibenzyl[9] (**4**, 82% yield). The analytical sample was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 185 °C, 90 ml/min He]: NMR ($CDCl_3$) δ 2.95 (m, 4, CH_2), 7.25 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{13}Br$: C, 64.38; H, 5.02. Found: C, 64.17; H, 5.03.

When reaction was effected with 2 equiv of *n*-butyllithium, the only product detected was bibenzyl [**7**, 86% yield, mp 50.5–52 °C (lit.[10] mp 51.5–52.5 °C); NMR ($CDCl_3$) δ 2.95 (s, 4, CH_2), 7.25 (m, 10, aromatic H)].

Reaction of o-iodobenzyl bromide[11] with *n*-butyllithium was carried out as for **1**, except that the reaction mixture was stirred for 30 min at −100 °C prior to quenching with water (~75 ml) and ether (~100 ml). The dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to afford 3.21 g of yellow oil. The crude product was distilled in vacuo to give (a) 0.57 g [37%, bp 76–86 °C (0.03 Torr)] of nearly pure (GLC, coinjection of an authentic sample) bibenzyl, and (b) 1.57 g [bp 95–110 °C (0.03 Torr)] of impure 2-iodobibenzyl. The material was obtained pure by recrystallization from a mixture (80:20) of petroleum ether[12a] and chloroform to afford 0.78 g of **6** (30%): mp 71.5–75 °C [lit.[13] bp 175 °C (0.5 Torr)]; NMR ($CDCl_3$) δ 3.10 (s, 4, CH_2), 7.25 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{13}I$: C, 54.57; H, 4.25. Found: C, 54.48; H, 3.91.

Reactions of o-Bromobenzyl Chloride[14] (8). A. Conversion to Benzyl Chloride. Analysis of an aliquot[17] obtained from **8** (0.025 mol) and *n*-butyllithium (0.025 mol) at −100 °C 10 min after mixing showed (NMR) essentially only benzyl chloride. The entire mixture was added to a mixture of water (50 ml) and ether (200 ml). Benzyl chloride [88% yield, bp 177–180 °C (lit.[18] bp 179 °C)] was obtained by distillation of the dried organic extract.

B. Spiro[cyclohexane-1,1′-phthalan] (10). The above mixture prepared from **8** (0.05 mol) was treated at −100 °C with *n*-butyllithium (0.05 mol) followed by cyclohexanone (0.075 mol); the resulting mixture was allowed to warm to 25 °C and was poured into water (~100 ml). The organic material obtained from the dried ether extract was distilled in vacuo to give 7.9 g (84% yield) of **10**: bp 87–89 °C (0.01 Torr); pure by GLC; NMR ($CDCl_3$) δ 1.7 (broad s, 10, aliphatic H), 5.1 (s, 2, CH_2O), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.85; H, 8.62.

C. Preparation of *N*-Phenylphthalimidine (11). Reaction was carried out as in A above; the mixture was stirred for 40 min at −105 °C, phenyl isocyanate (5.95 g, 0.05 mol) in hexane[7] (~25 ml) was added, and the reaction mixture was allowed to warm to room temperature. The entire mixture was added to water (~100 ml) and ether (~200 ml) and the dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to afford 8.44 g of pink semisolid. The crude product was recrystallized twice from a mixture (80:20) of petroleum ether[12b] and chloroform to give 3.82 g (**11**, 73%, mp 156–158 °C, lit.[19] mp 160 °C) of nearly pure **11**. The material

was obtained pure by two successive recrystallizations; mp 166–167 °C; NMR ($CDCl_3$) δ 4.95 (s, 2, CH_2), 7.80 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.36; H, 5.38; N, 6.63.

D. Conversion to 9,10-Dihydroanthracene (12). The reaction was carried out as in A above; the mixture was processed by a variety of procedures to detect benzocyclopropene[4,20] (**13**, NMR[21] δ 3.11, CH_2). In a typical experiment the mixture was allowed to warm to 25 °C (~3 h); anions were decomposed by addition of water (~5 ml) and the solution was dried ($MgSO_4$, excess). In one experiment, low-boiling materials (identified by NMR spectral analysis as THF, hexane, and *n*-butyl bromide) were removed at 45 °C (150 Torr). The residue contained 9,10-dihydroanthracene and benzyl chloride in the ratio of 70:30 [NMR ($CDCl_3$) δ 3.9 and 4.5, respectively for CH_2 (singlets)]. Recrystallization of the residue from petroleum ether[12a] or ethanol gave pure 9,10-dihydroanthracene (**12**, 0.97 g, 43% yield, mp[22] and mmp 108–110 °C).

Reactions of *o*-Bromophenethyl Bromide (14). A. Phenethyl Bromide. Reactions of **14**[23] [0.03 mol, prepared in 83% yield by reaction of *o*-bromophenethyl alcohol[24] with hydrobromic acid (48%)] with *n*-butyllithium (0.03 mol) at −100 °C was complete <5 min after mixing. Analysis of aliquots[8] showed only phenethyl bromide[25] and benzocyclobutene, in the ratio of 97:3, to be present.

B. Spiro[cyclohexane-1,1′-isochroman] (17). The solution of **15** (0.03 mol), prepared as in A, above, was treated at −105 °C with cyclohexanone (0.04 mol) and the resulting mixture was allowed to warm to 20 °C. The mixture was added to water (~100 ml) and was extracted with ether. The oil obtained from the dried ($MgSO_4$) ether extract was distilled in vacuo to give pure **17**: bp 110–115 °C (0.07–0.09 Torr); NMR ($CDCl_3$) δ 1.7 (m, 10, aliphatic H), 2.9 (t, 2, $ArCH_2$), 4.05 (t, 2, CH_2O), 7.5 (m, 4, aromatic H)].

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.92; H, 9.13.

C. Benzocyclobutene (18). A solution of **15** (0.0189 mol), prepared as described in A above, was stirred for 0.5 h at −100 °C and allowed to warm to 25 °C. The resulting mixture was added to water (~100 ml) and the organic products were collected by extraction with ether. The crude product (2.67 g) was distilled to give 1.57 g of a clear, colorless oil [bp 77 °C (70 Torr)]. Spectral analysis (NMR) of the oil showed it to be a mixture of benzocyclobutene (**18**, 80%, 68% yield), tetrahydrofuran (5%), and *n*-butyl bromide (15%). Pure benzocyclobutene[6] was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 150 °C, 90 ml/min He]: NMR ($CDCl_3$) δ 3.18 (s, 4, CH_2), 7.10 (m, 4, aromatic H); ir 1450, 1010, 775, 720 cm^{-1}; molecular ion *m/e* 104; $n^{23}D$ 1.5411 (lit.[26] $n^{25}D$ 1.5409).

Anal. Calcd for C_8H_8: C, 92.96; H, 7.74. Found: C, 92.34; H, 7.70.

Reaction of γ-(*o*-Bromophenyl)propyl Bromide (19) with *n*-Butyllithium. Formation of Indan (21). Reaction of **19** [0.025 mol, prepared from β-(*o*-bromophenyl)propanoic acid[2c] by reduction to γ-(*o*-bromophenyl)propanol (90% yield, bp 100–105° (0.02–0.01 Torr), lit.[27] bp 106–108 °C (0.5 Torr), with lithium aluminum hydride and subsequent conversion of the alcohol to **19** (81% yield, bp 104–108 °C (0.6–0.5 Torr), lit.[27] bp 84–85 °C (0.3 Torr), with hydrobromic acid (48%)] with *n*-butyllithium (1 molar equiv) at −100 °C was complete after 15 min (aliquots[28] indicated only indan). The mixture was decomposed with water (50 ml) and processed by extraction (ether) and the dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to give a residue which was distilled in vacuo to afford 2.42 g [**21**, 82% yield, bp 176–177 °C, lit.[29] bp 177 °C (760 mm)] of pure indan: NMR ($CDCl_3$) δ 2.05 (m, 2, $-CH_2$), 2.92 (t, 4, $-CH_2$), 7.2 (m, 4, aromatic H).

Anal. Calcd for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.52; H, 8.41.

Reactions of γ-(*o*-Bromophenyl)-1-propyl Chloride[30] (22). A. Conversion to 3-Chloro-1-phenylpropane (24). Studies of aliquots[28] obtained 15 min after the addition of *n*-butyllithium (1 molar equiv) to **22** (1 molar equiv) at −100 °C showed no starting material and only **24**. The entire product was added to water and the organic residue obtained from the dried ($MgSO_4$) ether extract was distilled to give pure **24** (81% yield, bp 218–220 °C, lit.[31] bp 219–220 °C).

B. Conversion to Indan (21). When the solution of **23**, prepared at −100 °C, was warmed to 20 °C (24 h) prior to addition of water, pure indan (**21**, 78% yield, bp 176–177 °C[29]) was obtained.

C. Conversion to 25. The solution of **23** (0.05 mol) prepared as in A was treated at −100 °C with cyclohexanone (2 molar equiv) at −100 to −90 °C and the resulting mixture was allowed to warm to 25 °C (24 h). The crude product (obtained by addition to water with subsequent extraction with ether) was distilled through a short Vigreux column to give cyclohexanone containing some **25** (bp <100°, 0.04 Torr). The column was replaced by a short-path column and nearly pure **25** [8.1 g, 64% yield, bp 140–145 °C (0.04 Torr)] was collected. Fractionation of this material through a short Vigreux column gave the analytical sample: bp 153–156 °C (0.03 Torr); NMR ($CDCl_3$) δ 1.8 (m, 13, aliphatic H), 3.2 (m, 2, $-CH_2$), 3.65 (t, 2, $-CH_2$), 7.35 (m, 4, aromatic H).

Anal. Calcd for $C_{15}H_{21}ClO$: C, 71.21; H, 8.37; Cl, 14.03. Found: C, 71.51; H, 8.48; Cl, 13.75.

Registry No.—**1**, 3433-80-5; **4**, 57918-64-6; **5**, 40400-13-3; **6**, 35444-96-3; **7**, 103-29-7; **8**, 578-51-8; **10**, 171-80-2; **11**, 5388-42-1; **12**, 613-31-0; **14**, 1074-15-3; **15**, 57918-65-7; **17**, 57918-66-8; **18**, 694-87-1; **19**, 1075-28-1; **21**, 496-11-7; **22**, 57918-67-9; **23**, 57918-68-0; **24**, 104-52-9; **25**, 57918-69-1; *n*-butyllithium, 109-72-8; cyclohexanone, 108-94-1; phenyl isocyanate, 103-71-9.

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(14) Prepared [74% yield, bp 73–74 °C (0.2 Torr), lit.[15] bp 110–111 °C (15 Torr)] from *o*-bromobenzyl alcohol[16] by reaction with thionyl chloride.
(15) J. B. Conant et al., *J. Am. Chem. Soc.*, **47**, 488 (1925).
(16) W. E. Parham and D. Egberg, *J. Org. Chem.*, **37**, 1545 (1972).
(17) The benzylic protons of *o*-bromobenzyl chloride and benzyl chloride appear as sharp singlets at δ 4.65 and 4.50, respectively.
(18) W. H. Perkin, *J. Chem. Soc.*, **69**, 1203 (1896).
(19) J. Hessert, *Ber.*, **10**, 1450 (1877).
(20) W. Billups, A. Blakeney, and W. Chow, *Chem. Commun.*, 1461 (1971).
(21) E. Vogel, W. Grimme, and S. Korte, *Tetrahedron Lett.*, **41**, 3625 (1965).
(22) E. Bamberger and W. Lodter, *Ber.*, 20, 3073 (1887).
(23) V. D. Sontag, *Ann. Chim. (Paris)*, **1**, 359 (1934).
(24) S. Uyeo, T. Mizutani, A. Yoshitake, and A. Ito, *Yakugaku Zasshi*, **84**, 458 (1964).
(25) Authentic material was prepared in 83% yield by reaction of phenethyl alcohol with hydrobromic acid (48%), bp 52–54 °C (0.03 Torr) [lit.[23] bp 93–96 °C (13 Torr)].
(26) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **78**, 500 (1956).
(27) M. H. Beeby and F. G. Mann, *J. Chem. Soc.*, 411 (1951).
(28) Spectral analysis (NMR).
(29) W. H. Perkin, *J. Chem. Soc.*, **69**, 1249 (1896).
(30) Prepared (71% yield) from reaction of γ-(*o*-bromophenyl)propanol[27] with thionyl chloride, bp 90–94 °C (0.3–0.4 Torr). Anal. Calcd for $C_9H_{10}BrCl$: C, 46.28; H, 4.32; Br, 34.22. Found: C, 46.35; H, 4.41; Br, 34.06.
(31) G. Errara, *Gazz. Chim. Ital.*, **16**, 313 (1886).

Elaboration of Bromoarylnitriles[1]

William E. Parham* and Lawrence D. Jones

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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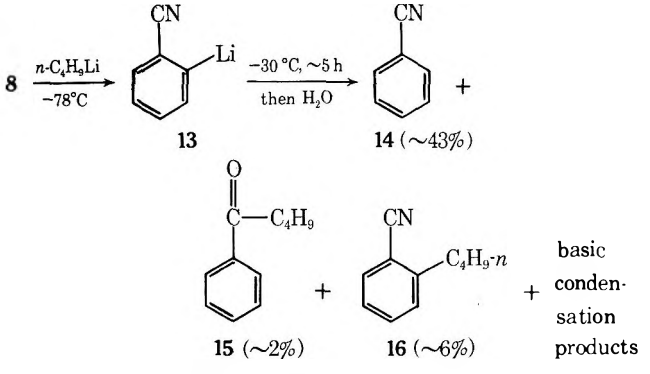
n-Butyllithium reacts selectively at −100 °C with the isomeric bromobenzonitriles by halogen–metal exchange. The resulting lithiobenzonitriles are stable at −100 °C and can be elaborated with electrophiles to give good yields of substituted benzonitriles, or, in the case of *o*-bromobenzonitrile, cyclic products derived from them. Studies of reactions of bromobenzylnitriles and bromophenylpropionitriles with *n*-butyllithium at −100 °C are also described.

The preparation of aryllithium reagents from isomeric bromobenzonitriles by halogen–metal exchange with *n*-butyllithium has been reported;[2] however, such derivatives have not been useful as synthetic intermediates. The low yields[2] of functionalized products obtained by reaction of such lithioarene intermediates with electrophiles are due, at least in part, to the reactivity of the nitrile function with organometallic reagents. The recent observation that bromine–lithium exchange can be effected selectively at −100 °C with aryl bromides containing carboxylate[3a] and, with limitations,[3b] methyl ester functions suggested that bromobenzonitriles could be efficiently elaborated at very low temperature. This has been shown to be the case.

The isomeric bromobenzonitriles were treated in tetrahydrofuran–hexane with *n*-butyllithium at −100 °C. In the case of *o*-bromobenzonitrile, essentially identical results were obtained at −78 °C; halogen–metal exchange was complete[4a] in 5 min at −100 °C. The derived lithioarene intermediates were then functionalized by addition of suitable electrophiles. The results, summarized in Table I, are self-explanatory; however, attention should be called to the fact that intramolecular cyclizations of product anions with the adjacent nitrile functions generally occurred in the ortho series.

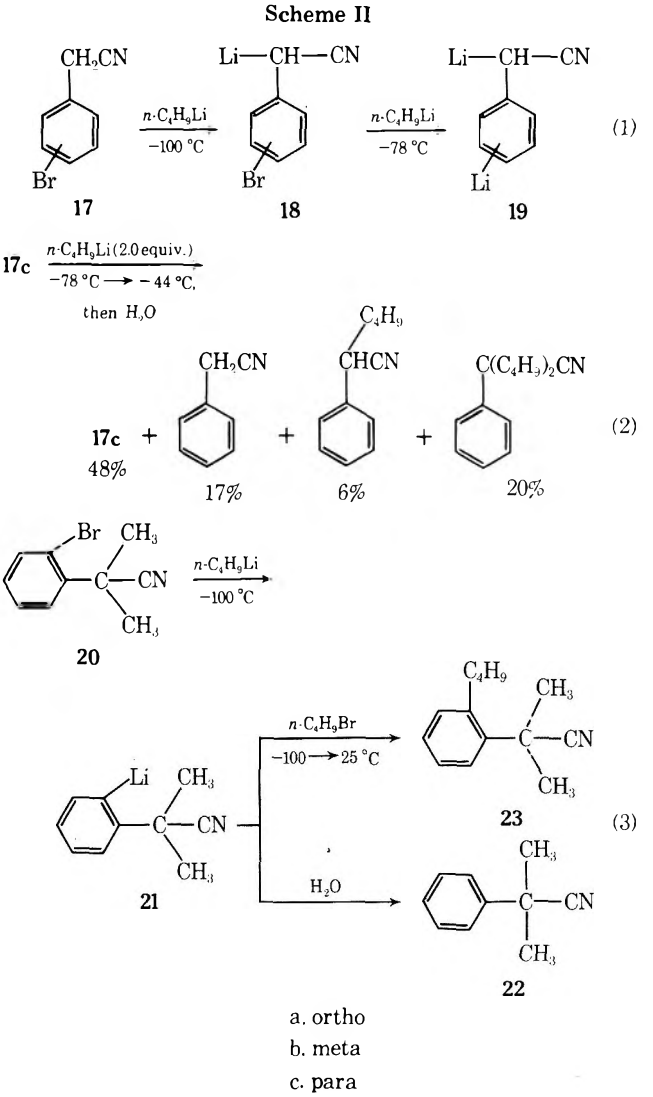
The stability of the derived lithiobenzonitriles was examined briefly by warming *o*-lithiobenzonitrile, subsequent to its formation at −78 °C, for 5 h at −30 °C prior to the addition of water. The products, shown in Scheme I,

Scheme I



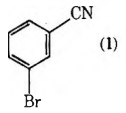
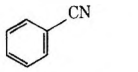
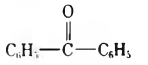
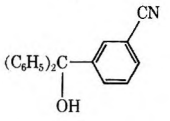
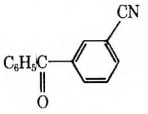
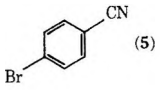
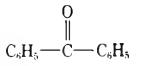
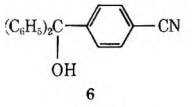
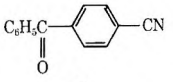
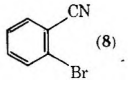
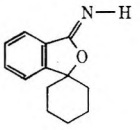
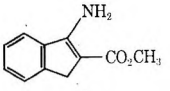
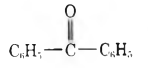
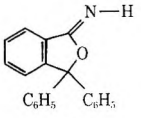
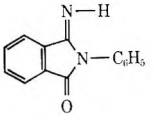
suggest that (1) the lithium derivative, once formed, is reasonably stable (~43% of **14**), and (2) reaction of the lithium reagent with *n*-butyl bromide, formed during the exchange reaction, becomes significant (~6% of **16** plus butylated condensation products) at higher temperatures. The formation of significant quantities of higher molecular weight basic condensation products is assumed to result, in part, by condensation of **13** with **16** and with itself. While the mixture of condensation products was not resolved,[6] samples were hydrolyzed with hydrochloric acid and with alkali. No anthraquinone was detected in the resulting products.[7]

Scheme II



It was of interest to determine whether or not anions derived from homologous bromobenzylnitriles would undergo halogen–metal interchange (Scheme II). Reaction of **17** with *n*-butyllithium at −100 °C gave **18**;[8] however, the anionic character of the benzylic carbon in **18** inhibited halogen–metal exchange in **18** at −100 °C with excess *n*-butyllithium. Examination of aliquots[4a] treated with water after 1 h at −100 °C obtained when excess *n*-butyllithium was employed showed ratios of benzylnitrile to unchanged bromobenzylnitrile of 3.5/97, 1/99, and 0.5/99.5 for **17a**, **17b**, and **17c**, respectively. There was no appreciable change in their ratios after an additional 2 h at −100 °C. Exchange was also slow at −78 °C (6.2, 7.2, and 5.0%, respectively for

Table I. Reaction of Isomeric Lithiobenzonitriles

Substrate	Reactant	Product	Isolated yield, %
 (1)	H_2O	 2	72
1		 3	86
1	$C_6H_5CO_2CH_3$	 4	33
 (5)	H_2O	**2**	82
5		 6	83
5	$C_6H_5CO_2CH_3$	 7	47[a]
 (8)		 9	82[b]
8	$CH_2{=}CHCO_2CH_3$	 10	9[c,d]
8		 11	50
8	C_6H_5NCO	 12	75[e]

[a] The order of addition of the lithiobenzonitrile and methyl benzoate did not affect the yield appreciably.[5] [b] Compound **9** was converted in high yield into the corresponding lactone by reaction with (a) hydrochloric acid, or (b) dilute aqueous sodium hydroxide followed by acidification. [c] Compound **10** was anticipated by intramolecular cyclization of the 1,4 adduct with subsequent enolization of the derived imino function. [d] The major organic residue was polymer, assumed to be formed from the product derived subsequent to 1,2 addition to the ester carbonyl group. [e] Compound **12** was isolated as *N*-phenylphthalimide.

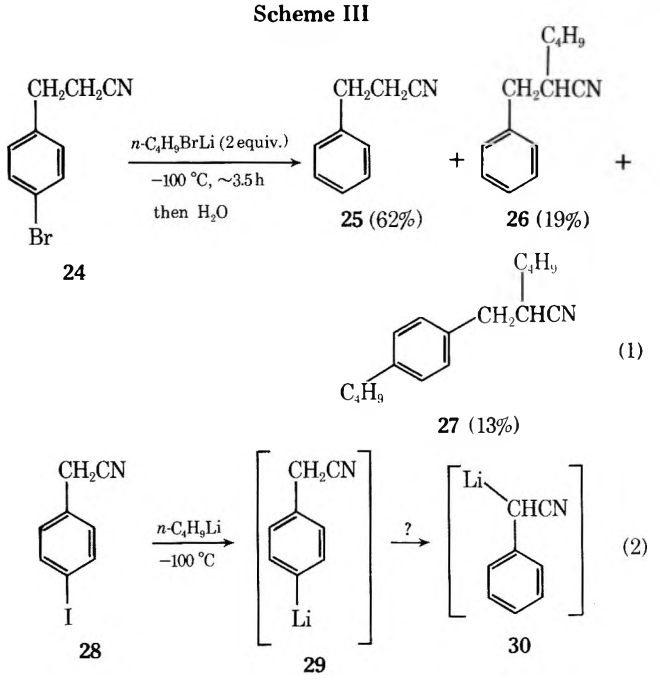
17a, 17b, and **17c** after ~4.5 h);[4a] however, some butylation occurred, presumably by reaction of **18** or **19** with *n*-butyl bromide, at −78 °C.

When reaction of **17** with *n*-butyllithium is carried out at higher temperatures (−44 °C), halogen–metal exchange is significantly increased; however, butylation of derived anions by *n*-butyl bromide, formed by exchange, becomes a significant side reaction. Thus, warming the product of reaction of **17c** with 2 equiv of *n*-butyllithium, formed at −78 °C, to −44 °C gave a product containing nitriles in the ratios shown in eq 2, together with three other components which were not examined.

When benzylic anion formation is disallowed, as in **20,** halogen–metal exchange is rapid (~100% yield after 10 min) and complete.[4a] Formation of α,α-dimethylbenzonitrile (**22,** ~100% yield) by addition of water to **21** suggests that bromobenzylic nitriles with no benzylic protons can be conveniently elaborated through the aryllithium intermediate. This was demonstrated by allowing the mixture prepared from **20** to warm to room temperature; α,α-dimethyl(*o*-butylbenzyl)nitrile (**23**) was formed by reaction of **21** with *n*-butyl bromide, formed by exchange, and was isolated pure in 74% yield.

When the alkylnitrile function in the arene is not benzylic, then halogen–metal exchange occurs readily (Scheme III). While the primary reaction of **24** with 1 equiv of *n*-butyllithium is anion formation at the methylene group adjacent to the nitrile function,[9] the anionic center is suffi-

Scheme III



ciently removed to permit complete halogen–metal exchange with the second equivalent of *n*-butyllithium. Such reactions are not, however, of synthetic interest since there are two anionic centers available for reaction with E^+. Such reactions are further complicated by the fact that appreciable butylation[10] occurs (**26** and **27**) even at −100 °C. It is also of interest to note that iodine–lithium exchange is sufficiently more rapid than bromine–lithium exchange to permit appreciable halogen–metal exchange in **28** (80%) in preference to proton removal with only 1 equiv of *n*-butyllithium (eq 2, Scheme III);[11] however, attempts to elaborate **29** and/or **30** formed from **28** and 1.5 equiv of *n*-butyllithium at −100 °C, with cyclohexanone, led to a complex unresolved mixture containing butylated products.

Experimental Section

Isomeric Bromobenzonitriles. General Procedure. Conversion of *m*-Bromobenzonitrile (1) to Benzonitrile (2). *m*-Bromobenzonitrile[12] (5.00 g, 0.0275 mol), tetrahydrofuran (~125 ml, freshly distilled over lithium aluminum hydride), and dry hexane[13] (~35 ml) were introduced, under nitrogen, into a three-neck flask equipped with a low-temperature thermometer, addition funnel, mechanical stirrer, and nitrogen inlet tube. The reaction mixture was cooled to −100 °C (liquid nitrogen–diethyl ether bath) and *n*-butyllithium (11.9 ml, 0.0275 mol, 2.3 M solution in hexane) was added rapidly (the rate of addition was adjusted such that the temperature did not momentarily exceed −92 °C). Examination of aliquots[4a] showed that halogen–metal exchange was complete <5 min after the addition of *n*-butyllithium (1 equiv). The reaction mixture was poured into water (~200 ml). The organic layer was separated, and the aqueous layer was extracted with three 100-ml portions of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated (rotary evaporation) to afford 3.10 g of light, yellow oil. This material was distilled to give 2.03 g [72%, bp 188–191 °C, lit.[14] bp 190.6 °C (760 mm)] of pure (GLC)[4a] benzonitrile.

Preparation of Diphenyl(*m*-cyanophenyl)carbinol (3). Reaction of **1** (0.0275 mol) in a mixture of THF (~125 ml)–hexane[13] (~35 ml) with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure. Benzophenone (0.0275 mol) in dry THF (~30 ml) was added; the reaction mixture was warmed to 20 °C and poured into water (100 ml). The organic layer was separated and the aqueous layer was extracted once with ether (100 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated to afford 8.65 g of yellow oil. The material was recrystallized once from petroleum ether[15a] to give 6.76 g (86% mp 87–92 °C) of nearly pure **3**. Elution of a portion (400 mg) of this material on a preparative silica gel plate (fluorescent indicator) with a mixture (80:20) of petroleum ether[15c] and ether afforded pure **3** (380 mg, 82%, mp 96.5–98.5 °C); ir ν_{OH} 3330, ν_{CN} 2170 cm^{-1}.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.23; H, 5.36; N, 4.85.

Preparation of 3-Cyanobenzophenone (4). Reaction of **1** (0.0275 mol) in a mixture of THF (~125 ml)–hexane[13] (~30 ml) with *n*-C_4H_9Li was carried out as described above. The reaction mixture was stirred at −100 °C for 10 min; an aliquot (~10 ml) was quenched with water and dried ($MgSO_4$), and examination of the residue by GLC (5% SE-30 on Chromosorb W, 3 ft × 0.25 in., 105 °C, 45 ml/min He] indicated complete conversion of **1** to 3-lithiobenzonitrile.[4a] Methyl benzoate (0.029 mol) in dry THF (~25 ml) was added; the reaction mixture was warmed to 25 °C and poured into water (100 ml). Ether extraction of the aqueous layer and concentration of the organic extracts afforded 5.72 g of yellow oil. The material was recrystallized twice from methanol to give 1.7 g [33%, mp 90–92 °C (lit.[16] mp 92 °C)] of pure 3-cyanobenzophenone.

Conversion of *p*-Bromobenzonitrile (5)[12] to Benzonitrile (2). Reaction of **5** (0.0275 mol) in a mixture of dry THF (~125 ml)–hexane[13] (~35 ml) with *n*-C_4H_9Li (0.0275 mol) and subsequent decomposition of *p*-lithiobenzonitrile with water was carried out as described for **1**. Distillation of the residue (3.02 g) gave 2.33 g (82%) of pure (GLC)[4a] benzonitrile.

Preparation of Diphenyl(*p*-cyanophenyl)carbinol (6). The procedure, starting with **5**, was essentially identical with that described for **3**. The crude product was crystallized from a mixture (85:15) of petroleum ether[15b] and chloroform to give 6.54 g (83% yield, mp 90–93 °C) of nearly pure **6** (mp 92–93.5 °C; ir (KBr) ν_{OH} 3300, ν_{CN} 2200 cm^{-1}).

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 83.97; H, 5.31; N, 4.80.

Preparation of 4-Cyanobenzophenone (7). The procedure, starting with **5**, was essentially identical with that described for **4**. One recrystallization of the crude product from methanol gave pure **7** (mp 115–116 °C, lit.[17] mp 107–108 °C).

Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.43; H, 4.41; N, 6.66.

Conversion of *o*-Bromobenzonitrile (8)[12] to Phthalan 9. Reaction of **8** (0.0275 mol) in THF (~125 ml)–hexane[13] (~40 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure, except that the reaction mixture was maintained at −78 °C (dry ice–acetone bath). Examination (GLC)[4a] of an aliquot (~10 ml) indicated only *o*-lithiobenzonitrile. Cyclohexanone (0.0296 mol) in THF (~20 ml) was added; the reaction mixture was warmed to 5 °C and was poured into ice-cold water (100 ml). Rapid extraction (chloroform) of the aqueous layer, followed by concentration of the organic extracts, gave 6.97 g of yellow oil. The crude product was distilled in vacuo to afford 4.5 g [82%, bp 104–105 °C (0.03 Torr)] of pure iminophthalan **9**: ir ν 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (broad s, 10 aliphatic H), 6.75 (broad s, 1, NH), 7.4 (m, 3, aromatic H), 7.85 (m, 1, aromatic H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.39; H, 7.35; N, 6.88.

Acid (concentrated hydrochloric) or base (10% sodium hydroxide) hydrolysis of phthalan **9** gave the corresponding known lactone[18] (mp, mmp 80–82 °C) in high yield.

Preparation of 2-Carbomethoxy-3-aminoindene (10). Reaction of **8** (0.0275 mol) in a THF (~125 ml)–hexane[13] (~40 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described above. Methyl acrylate[19] (0.030 mol) in dry hexane[13] (~25 ml) was added; the reaction mixture was warmed to 0 °C and poured into water (~100 ml). The crude product was distilled in vacuo to afford 1.47 g of yellow oil. The oil was recrystallized once from petroleum ether[15a] to give 0.45 g (9%, mp 103.5–105 °C) of pure **10**: NMR ($CDCl_3$) δ 3.62 (s, 2, benzylic H), 3.90 (s, 3, $-OCH_3$), 6.0 (broad s, 2, $-NH_2$), 7.5 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.09; H, 5.63; N, 7.30.

The distillation residue appeared to be polymeric.

Preparation of Phthalan 11. Reaction of **8** (0.0275 mol) in a THF (~125 ml)–hexane[13] (~35 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure. Benzophenone (0.028 mol) in THF (~25 ml) was added, and the reaction mixture was warmed to 0 °C and poured into cold water (~100 ml). Rapid extraction (ether) of the aqueous layer and concentration (rotary evaporation) of the organic extracts afforded 8.38 g of yellow solid. The crude product was recrystallized from petroleum ether[15a] to give 3.93 g (50%, mp 106–107.5 °C) of nearly pure iminophthalan **11**. One further recrystallization of this material gave the pure product, 2.56 g (33%, mp 108.5–109.5 °C); ir ν 1660 cm^{-1}.

Anal. Calcd for C_9H_8BrN: C, 51.45; H, 3.84; N, 6.67. Found: C, 51.31; H, 3.88; N, 6.70.

Preparation of *N*-Phenylphthalimide (12). Reaction of 8 (0.275 mol) in a THF (~125 ml)–hexane[13] (~35 ml) mixture with n-C_4H_9Li (0.0275 mol) was carried out as described above, except that the reaction mixture was maintained at −78 °C. Phenyl isocyanate (0.03 mol) was added; the reaction mixture was warmed to 25 °C and poured into dilute aqueous hydrochloric acid (5% ~150 ml) and the resulting mixture was allowed to stand for 2 h. Extraction (chloroform) of the aqueous layer and concentration of the organic extracts afforded 6.19 g of yellow semisolid. The crude product was recrystallized once from a mixture (85:15) of absolute alcohol and chloroform to give 4.6 g (75%, mp 206–210 °, lit.[20] mp 208 °C) of **12**.

Reaction of *o*-Bromobenzonitrile and *n*-Butyllithium at −30 °C. The reaction mixture, prepared as described in the general procedure using 1 equiv of n-C_4H_9Li at −78 °C, was allowed to warm to ~−30 °C and was maintained at this temperature for 5 h. The resulting product was added to cold concentrated hydrochloric acid (~200 ml) and separated into neutral and basic components by conventional methods. The isolated neutral component was analyzed by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 180 °C, 80 ml/min He; the components were identified by coinjection of authentic materials and/or by isolation] and was found to contain benzonitrile (1.13 min, ~43% yield), *o*-butylbenzonitrile [**16**, ~6% yield, 2.94 min; NMR ($CDCl_3$) δ 0.95 (t, 3, CH_3), 1.5 (m, 4, CH_2), 2.85 (t, 2, $ArCH_2$), 7.4 (m, 4, aromatic H); ir ν_{CN} 2200 cm^{-1}] and valerophenone [**15**, ~4% yield, 3.13 min; NMR ($CDCl_3$) δ 0.7–1.95 (m, 6, aliphatic H), 3.0 (t, 2, $ArCH_2$), 7.45 (m, 3, aromatic H), 8.00 (m, 2, aromatic H)]. The dark green solid (1.74 g) obtained by neutralization of the acidic fraction was multicomponent; attempts (recrystallization, TLC) to resolve this mixture into pure components were unsuccessful. Hydrolysis of the presumed imino functions with both ethanolic potassium hydroxide–water and with dilute hydrochloric acids gave mixtures (five colored bands on TLC); however, TLC experiments showed that no anthraquinone was present.

Preparation of the Isomeric Bromobenzylnitriles. *o*-Bromobenzylnitrile[21] [**17a**, NMR ($CDCl_3$) δ 3.82 (s, 2, CH_2)], *m*-bromobenzylnitrile[21] [**17b**, NMR ($CDCl_3$) δ 3.82 (s, 2, CH_2)], and *p*-bromobenzylnitrile[21] [**17c**, NMR ($CDCl_3$) δ 3.70 (s, 2, CH_2)] were prepared in good yield by conventional procedures from the corresponding bromobenzyl bromides. The bromobenzyl bromides were prepared from the corresponding bromotoluenes by bromination with *N*-bromosuccinimide[22] or from the corresponding bromobenzyl alcohol[23a] by reaction with aqueous hydrobromic acid (48%).[23b] The latter process was preferable since the nitriles obtained were free of trace impurities as determined by NMR and GLC analysis.

α,α-Dimethyl-*o*-bromobenzylnitrile (20). *o*-Bromobenzonitrile (**17a**, 20.0 g, 0.103 mol) dissolved in dimethylformamide (40 ml) was added slowly, under nitrogen, to a mixture of sodium hydride (5.2 g, 0.12 mol), dimethylformamide (40 ml), and benzene (20 ml) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and methyl iodide (17 g, 0.12 mol) was added slowly. The resulting mixture was warmed to 25 °C (~0.5 h) and poured into water (100 ml) and the aqueous layer was extracted with four 60-ml portions of chloroform. The oil [bp 103 °C (0.2 Torr)] obtained from the dried chloroform was dissolved in dimethylformamide (40 ml) and re-treated, as above, with sodium hydride and methyl iodide. The oil, obtained as described above, was distilled to give pure **20** [19.5 g, 87% yield; bp 95–105 °C (~0.03 Torr); NMR ($CDCl_3$) δ 1.9 (s, 6, CH_3), 7.4 (m, 4, aromatic H)].

Anal. Calcd for $C_{10}H_{10}BrN$: C, 53.60; H, 4.50; Br, 35.66; N, 6.25. Found: C, 53.43; H, 4.37; Br, 35.53; N, 6.15.

α-Butylphenylacetonitrile and α,α-Dibutylphenylacetonitrile. n-Butyllithium (13.3 ml, 0.032 mol, 2.4 M solution in hexane) was added dropwise to a cold (−78 °C, dry ice–acetone bath), stirred solution of phenylacetonitrile (7.5 g, 0.064 mol) in THF (100 ml, freshly distilled from lithium aluminum hydride) under an atmosphere of nitrogen. n-Butyl bromide (3.44 ml, 0.032 mol) was added rapidly. The mixture was warmed to 0 °C (5 min) and cooled to −78 °C, and the treatment with n-butyllithium and n-butyl bromide was repeated; the resulting mixture was warmed to room temperature and stirred for 7 h. The mixture was poured into water (60 ml) and the organic layer was collected in ether. Analysis of the oil (11.2 g) obtained from the dry ($MgSO_4$) ether extract by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 230 °C, 70 ml/min He] indicated three components in the ratio of 74:21:5 [phenylacetonitrile (1.31 min, ~7.5% yield), α-butylphenylacetonitrile (3.12 min, ~75% yield), and α,α-dibutylphenylacetonitrile (6.19 min, ~16% yield)]. The oil was fractionated and the fraction [6.54 g, bp 83–86 °C (0.07 Torr)] rich in butylated material was resolved by preparative GLC (column as described above) to give the following.

α-Butylphenylacetonitrile [NMR ($CDCl_3$) δ 0.6–2.0 (m, 9, aliphatic H), 3.7 (t, 1, methine H), 7.3 (s, 5, aromatic H)].

Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73. Found: C, 83.27; H, 8.19.

α,α-Dibutylphenylacetonitrile [NMR ($CDCl_3$) δ 0.6–2.0 (m, 18, aliphatic H), 7.3 (s, 5, aromatic H)].

Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11. Found: C, 83.88; H, 10.06.

Reactions of Isomeric Bromobenzylnitriles (17a–c) with *n*-Butyllithium. These reactions were carried out essentially as described for the isomeric bromobenzonitriles. Progress of reactions was followed by examining aliquots.[4a]

At −100 °C with 1 equiv of n-C_4H_9Li there was no evidence of halogen–metal exchange; only anions **18** were formed. Thus, addition of water to the product obtained from **17a** (5.0 g) resulted in recovery of only *o*-bromobenzylnitrile (4.52 g, 92% yield). Addition of methyl iodide (1 equiv) with subsequent warming of the mixture to 25 °C (2 h) gave, subsequent to distillation [bp 70–72 °C (0.05 Torr)] nearly pure (79%) 2-(*o*-bromophenyl)propionitrile. Analysis of the product by GLC [5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., 140 °C, 45 ml/min He] showed *o*-bromobenzylnitrile (trace) and α,α-dimethyl-*o*-bromobenzylnitrile (5%). Pure **2-(*o*-bromophenyl)propionitrile** [NMR ($CDCl_3$) δ 1.59 (d, 3, CH_3), 1.39 (q, 1, CH), 7.35 (m, 2, aromatic H), 7.65 (m, 2, aromatic H)] was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 170 °C, ~90 ml/min He].

Anal. Calcd for C_9H_8BrN: C, 51.46; H, 3.84; N, 6.66. Found: C, 51.40; H, 4.02; N, 6.63.

Reaction of 17 with 2 Equiv of n-C_4H_9Li. Results at −100 and −78 °C are described in the discussion. At higher temperatures extensive butylation of derived anions resulted. Examination of the product obtained by reaction of *p*-bromobenzylnitrile with n-butyllithium (2 equiv; initial reaction at −78 °C, then aged 90 min at −53 °C and 30 min at −44 °C) by GLC [5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., 130 °C, 45 ml/min He] obtained subsequent to the addition of water showed at least seven components. Four of these, together with their ratio, were identified by NMR and by coinjection of authentic samples (see eq 2, Scheme II, in the discussion).

Reaction of α,α-Dimethyl-*o*-bromobenzylnitrile (20) with n-C_4H_9Li. The reaction was carried out at −100 °C as described for **1**. Examination of aliquots (GLC) showed that halogen–metal exchange was complete in <10 min [the product obtained subsequent to addition of water was essentially pure α,α-dimethylbenzylnitrile (**22**, 100% yield)].[24] The solution was allowed to warm to room temperature and was stirred at 25 °C for 0.5 h prior to quenching with water. The oil, obtained in the usual way from the reaction mixture, was distilled to give essentially pure α,α-dimethyl-*o*-butylbenzylnitrile (**23**): bp 79 °C (0.02 Torr); molecular ion m/e 201; ir ν_{CN} 2200 cm^{-1}; NMR ($CDCl_3$) δ 0.85–1.75 (m, 7, aliphatic H), 1.65 (s, 6, CH_3), 2.15 (m, 2, CH_2), 7.95 (m, 4, aromatic H). The sample submitted for analysis was collected by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 180 °C, 70 ml/min He].

Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.76; H, 9.66.

β-(*p*-Bromophenyl)propionamide was prepared from β-(*p*-bromophenyl)propionic acid[26] in a conventional way with thionyl chloride followed by ammonium hydroxide (85%, mp 138.5–141.5 °C). An analytical sample was obtained pure by recrystallization from a mixture (80:20) of petroleum ether[15a] and chloroform, mp 147–148 °C.

Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14; Br, 35.04. Found: C, 47.11; H, 4.40; N, 6.14; Br, 35.22.

β-(*p*-Bromophenyl)propionitrile (24) was prepared from the corresponding amide by dehydration with thionyl chloride [7 h reflux, 84% yield, bp 116 °C (0.05 Torr)].

Anal. Calcd for C_9H_8BrN: C, 51.45; H, 3.84; N, 6.67. Found: C, 51.31; H, 3.88; N, 6.70.

Reaction of β-(*p*-Bromophenyl)propionitrile (24) with n-C_4H_9Li. The reaction was carried out at −100 °C as described for **1**. Aliquots were decomposed with water and the products were analyzed by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 195 °C, 90 ml/min He]. With ~1 equiv of n-C_4H_9Li, the

ratio of **25/24** was 17/83 after 15 min; the ratio did not change after an additional 40 min at −100 °C. An additional 1.1 equiv of *n*-butyllithium was added. After 15 min the above ratio was 75/16; compound **26** was also detected. The mixture was continually stirred at −100 °C; examination of aliquots showed that the amount of **24** decreased while the amount of butylated products (**26** and **27**) increased. The mixture was quenched with water after a total of 4 h after the second addition of n-C_4H_9Li. The mixture of products obtained contained phenylpropionitrile (**25**, 62%), α-butyl-β-phenylpropionitrile (**26**, 19%), α-butyl-β-(*p*-butylphenyl)propionitrile (**27**, 13%), and an unidentified product. Products were collected by preparative GLC.

α-Butyl-β-phenylpropionitrile (26): NMR ($CDCl_3$) δ 0.9 (t, 3, aliphatic H), 1.55 (m, 6, aliphatic H), 2.9 (m, 3, aliphatic H), 7.3 (m, 5, aromatic H).

Anal. Calcd for $C_{13}H_{17}N$: C, 83.37, H, 9.15; N, 7.48. Found: C, 83.55; H, 9.05; N, 7.55.

α-Butyl-β-(*p*-butylphenyl)propionitrile (27): NMR ($CDCl_3$) δ 0.70–1.9 (m, 16, aliphatic H), 2.2 (m, 2, CH_2), 2.85 (m, 3, aliphatic H), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 83.79; H, 10.60.

***p*-Iodobenzylnitrile (28).** Examination[4b] of an aliquot, quenched with water taken after 15 min from reaction of 28[27] with 1 equiv of n-C_4H_9Li at −100 °C, showed the ratio of benzylnitrile to starting material (28) to be 80/20; starting material immediately disappeared upon addition of an additional 0.5 equiv of n-C_4H_9Li. Attempts to trap the anionic products from the reaction mixture with cyclohexanone gave a multicomponent mixture (GLC) which was not resolved.

Registry No.—**1**, 6952-59-6; **2**, 100-47-0; **3**, 57775-02-7; **4**, 6136-62-5; **5**, 623-00-7; **6**, 57808-43-2; **7**, 1503-49-7; **8**, 2042-37-7; **9**, 57775-03-8; **10**, 28873-85-0; **11**, 57775-04-9; **12**, 34446-14-5; **15**, 1009-14-9; **16**, 57775-05-0; **17a**, 19472-74-3; **17b**, 31938-07,5; **17c**, 16532-79-9; **20**, 57775-06-1; **23**, 57775-07-2; **24**, 57775-08-3; **26**, 54321-42-5; **27**, 57775-09-4; **28**, 51628-12-7; *n*-butyllithium, 109-72-8; benzophenone, 119-61-9; methyl benzoate, 93-58-3; cyclohexanone, 108-94-1; methyl acrylate, 96-33-3; phenyl isocyanate, 103-71-9; phenylacetonitrile, 140-29-4; *n*-butyl bromide, 109-65-9; α-butylphenylacetonitrile, 3508-98-3; α,α-dibutylphenylacetonitrile, 3508-99-4; 2-(o-bromophenyl)propionitrile, 57775-10-7; β-(*p*-bromophenyl)propionamide, 57775-11-8; β-(*p*-bromophenyl)propionic acid, 1643-30-7.

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(2) H. Gilman and G. Melstrom, *J. Am. Chem. Soc.*, **70**, 4177 (1948).
(3) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051 (1974); (b) *ibid.*, **39**, 2053 (1974).
(4) The degree of metalation was determined by treating aliquots with water and analyzing the dried organic products by (a) GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., or 5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., including injection of authentic starting halides and reduced products], (b) NMR, the benzylic protons of *p*-iodobenzyl nitrile and benzyl nitrile appear as sharp singlets at δ 3.75 and 3.65, respectively.
(5) Dr. Robert Piccirilli, Duke University, private communication.
(6) Thin layer chromatography showed it to be multicomponent.
(7) Imino anthraquinones (or *N*-butyl derivatives) were anticipated as possible products of self-condensation of **13** by analogy to products of self-condensation of lithium *o*-lithiobenzoates (cf. ref 3b).
(8) Reaction of **18a**, formed from **17a** and 1 equiv of *n*-butyllithium, with methyl iodide, gave a 79% yield of nearly pure 2-(*o*-bromophenyl)propionitrile (see Experimental Section).
(9) Analysis of the organic products obtained by decomposition of aliquots with water showed 17% halogen–metal exchange after 0.5 h with 1 equiv of *n*-butyllithium.
(10) Butylation is assumed to occur by reaction of *n*-butyl bromide, formed by exchange, with the dilithio derivative formed from **24**.
(11) Studies of aliquots showed that 80% iodine–lithium exchange occurs when **28** is treated with 1 equiv of *n*-butyllithium.
(12) *o*-, *m*-, and *p*-bromobenzonitrile are commercially available.
(13) Practical grade stored over molecular sieves.
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(24) Shown by coinjection of an authentic sample prepared from benzyl nitrile (1 equiv), sodium hydride (2 equiv), and methyl iodide (2 equiv) in dimethylformamide; bp 226 °C (754 mm); $n^{25}D$ 1.5016 (lit.[25] bp 232 °C; nD 1.50665).
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Ring Cleavage Rearrangements of 2-Bicyclo[3.2.0]heptyl and Related Grignard Reagents

E. Alexander Hill,* Robert J. Theissen,[1a] Charles E. Cannon,[1b] Richard Miller, Richard B. Guthrie, and Augustin T. Chen[1c]

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

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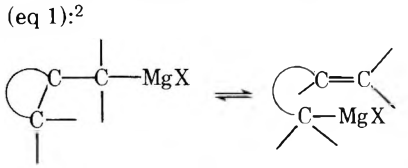
The Grignard reagent (**12**) from 2-bromobicyclo[3.2.0]heptane undergoes a ring cleavage rearrangement to cyclopentenylethyl (**13**) and cycloheptenyl (**14**) Grignard reagents. Grignard **14** is slowly converted to **13**. The rate of rearrangement of **12** is thought to be somewhat retarded by geometric restrictions introduced by the bicyclic skeleton. The facility of the rearrangement of **12** → **14** may indicate that the preferred transition state for rearrangement is nonplanar. Rearrangement of the Grignard reagent **25** from 3-chlorotricyclo[5.3.0.0^{2,6}]decane occurs in analogous fashion. Grignard reagents **31** from 2-bromo-6-alkoxybicyclo[3.2.0]heptanes decompose with elimination of the alkoxy group and ring cleavage to 3-vinylcyclopentene and 1,4-cycloheptadiene.

The rearrangement of appropriate organomagnesium compounds, either by cleavage of a strained ring or its reverse (intramolecular addition to a multiple bond), is well established (eq 1):[2]

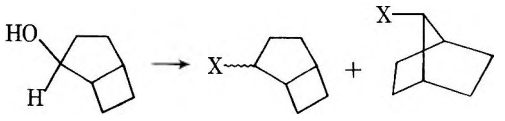


(1)

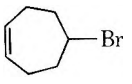
Experimental results have been interpreted as being most consistent with a synchronous four-center process for this rearrangement.[2-4] In the present paper, we report Grignard cleavage studies in the bicyclo[3.2.0]heptyl and tricyclo[5.3.0.0^{2,6}]decyl systems. These studies were undertaken to probe the effects of geometric constraints imposed on the transition state by the bicyclic system, and to assess the influence of a polar substituent, an alkoxy group.

Preparation of Halides. Bicyclo[3.2.0]heptan-2-ol (**1**)

was synthesized as reported by Winstein and Stafford.[5] Reaction of the alcohol with thionyl chloride in pyridine yielded a mixture containing *exo*-2-chlorobicyclo-[3.2.0]heptane and 7-chloronorbornane in a ratio of about 1:2. Bromide formation with bromine and triphenylphosphine was more successful in producing product without rearrangement. *endo*-2-Bromobicyclo[3.2.0]heptane, *exo*-2-bromobicyclo[3.2.0]heptane, and 7-bromonorbornane were formed in a ratio of 5:2:1, respectively. The mixture could be resolved by gas chromatography, but was used without separation for the Grignard studies.



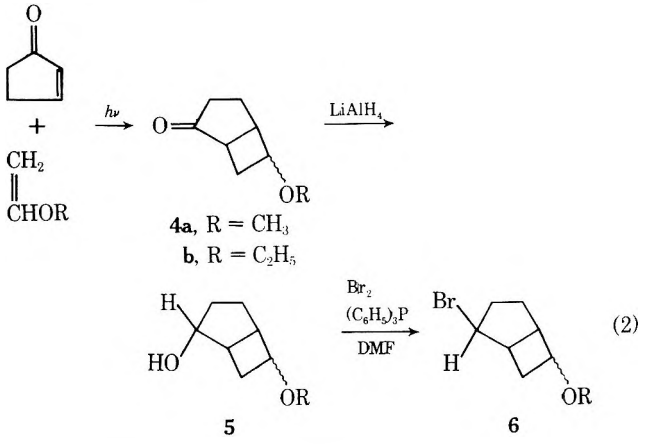
1 2a, X = Br; b, X = Cl



3

5-Bromocycloheptene (**3**) was synthesized from the corresponding alcohol.[6] It also contained a small amount (~10%) of 7-bromonorbornane, undoubtedly produced via carbonium ion rearrangement in the reaction of the alcohol with phosphorus tribromide.

The photochemical cycloaddition of cyclopentenone to methyl or ethyl vinyl ether produced the corresponding 6-alkoxybicyclo[3.2.0]heptan-2-ones **4**, which were converted to the respective bromides **6** (eq 2). Each of the compounds

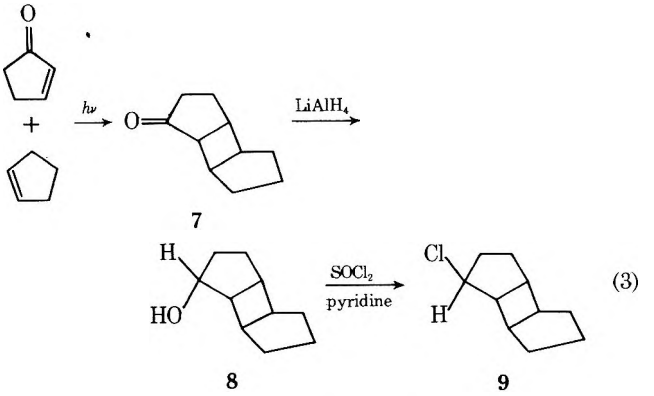


4a, R = CH_3; **b**, R = C_2H_5

5 **6** (2)

4–6 was obtained as a mixture of two isomers present in nearly equal amounts. These are epimers differing in configuration at the alkoxy group, rather than a mixture of 6- and 7-alkoxy derivatives, since either Wolff–Kishner reduction of ketones **4a** or **4b** or tri-*n*-butyltin hydride reduction of **6a** led to a mixture of saturated bicyclic ethers, rather than a single ether product. Hydrolysis of the Grignard reagent from **6a** or **6b**, or reduction of **6a** with sodium in alcohol, led to a mixture which contained unsaturated components also, as a result of disproportionation and/or elimination. The epimers of **4–6** were separated on a small scale for spectroscopic characterization, but most of the work was done with the mixture. Attempted preparation of the chloride corresponding to **6b** (thionyl chloride–pyridine) led to a mixture of products, including one lacking the ethoxy group, and was not pursued further.

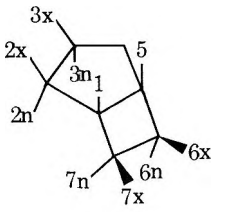
Tricyclo[5.3.0.$0^{2,6}$]decan-3-one (**7**), prepared by photocycloaddition of cyclopentenone to cyclopentene,[7] was reduced and converted to the chloride **9** (eq 3).



7 **8** **9** (3)

Stereochemical Considerations. From the results of x-ray crystallographic[8] and electron diffraction[9] studies, it appears that there is a pronounced tendency toward twisting or folding of the five-membered ring of the bicycloheptyl and tricyclodecyl systems. Folding of the four-membered ring is also likely. The precise manner of distortion from planarity may depend upon substitution and unsaturation present, as well as crystal forces in the x-ray studies.

NMR spectra provide further evidence for nonplanar geometry, and also for the configuration of substituents. In the 2-substituted bicyclo[3.2.0]heptanes, H-2n generally appears as a doublet,[10] with J_{2n-3n} as the only coupling of significant magnitude (see **10**). In the present work, dou-



10

blet absorption was noted for alcohol **1** and halides exo-**2a**, **6**, and **9** ($J \sim 3$–4 Hz). Small values for J_{2n-1} and J_{2n-3x} are found also in unsaturated analogues.[11] These require a conformation in which carbon 2 is rotated in the exo direction and carbon 3 endo, in order to obtain the implied dihedral angles of about 90°. With an endo 2 substituent, coupling of H-2x is more extensive. In the present work, spectra of alcohols **5** and **8** showed absorption resembling a broadened first order (1–3–3–1) quartet, suggesting coupling to three hydrogens (1, 3x, 3n) with similar coupling constants of 7–8 Hz. Similar results have been reported for some more heavily substituted or unsaturated analogues,[10b,11,12] though a different interpretation has also been given.[10a]

The configurations of compounds in this study are consistent with chemical expectations, as well as with the NMR spectra. Thus, reaction of **1** with thionyl chloride gives largely carbonium ion rearrangement to 7-chloronorbornane; most of the product of unrearranged structure appears to be exo isomer, formed with retention of configuration. Reaction with triphenylphosphine dibromide gives much less rearrangement, and most of the unrearranged product is now formed with inversion (endo), as expected from the greater tendency of this reagent to react by direct displacement. Reaction of **1** with triphenylphosphine–carbon tetrachloride also gives unrearranged endo isomer, but much more rearrangement.[10a] In the preparative sequence of eq 2 and 3, hydride reduction of ketones occurs as expected from the exo direction to yield endo alcohol. Conversion to halides without rearrangement was much more successful, since displacement by halide ion can occur from the less hindered exo side of the ring, and the C–C bond

Table I. Rearrangement Rates of Bicyclo[3.2.0]heptyl and Related Grignard Reagents in Ether

Grignard rearrangement	Concn, M	Temp, °C	$10^6 k$, s^{-1} [a]	k_{rel} (100 °C)
12 → 13	0.16	87.6	4.68 ± 0.09	0.059 [b]
		102.7	29.9 ± 0.7	
		114.6	104 ± 4	
	0.23	79.6	1.9	
		91.8	16	
		106.6	53	
	0.65	112	~50	
12 → 14	0.16	87.6	0.45	5×10^{-3} [c]
		102.7	2.4	
		114.6	7.3	
14 → 13	0.16	114.6	~2	$\sim 10^{-3}$
	~1	110	~0.3	
		125	~3.5	
exo-**31b → 32 + 33**	0.4	80	~80	~2
endo-**31a → 32 + 33**	0.4	76	>800	>40
25 → 26	~1	110	~1	$\sim 10^{-3}$
16a	0.145	66–80		1.68 [d]
16b	0.06	66–94		(1.00) [d,e]

[a] Error limits where given are standard deviations from a least-squares correlation. Errors in other rates are probably about ±10%, unless otherwise indicated as approximate. [b] $\Delta H^{\ddagger} = 31.6 \pm 0.9$ kcal/mol; $\Delta S^{\ddagger} = 4.3 \pm 1.5$ eu. [c] $\Delta H^{\ddagger} = 28$ kcal/mol, $\Delta S^{\ddagger} = -10$ eu. [d] Reference 17. [e] $\Delta H^{\ddagger} = 31.9 \pm 0.7$ kcal/mol, $\Delta S^{\ddagger} = 11 \pm 1$ eu.

that would have to be involved in a rearrangement to a norbornyl skeleton is no longer situated anti to the departing OH function. In NMR spectra of Grignard reagents prepared in this study, H-2 gave a poorly resolved multiplet, probably consistent with the anticipated mixture of exo and endo configurations of the magnesium halide function.

The configuration at C_6 (or C_7) is less satisfactorily established on the basis of coupling patterns of H-6n and H-6x. There are differences in coupling constants apparent in the spectra of unsaturated and more highly substituted compounds,[13] but the multiplets for compounds in eq 2 are complex and poorly resolved, precluding any really definitive distinction from coupling patterns. On the other hand, there does appear to be a consistent chemical shift difference, with either a hydrogen or methyl appearing at higher field when in the endo position.[13,14] Interestingly, exo and endo methoxy groups appear to have the same shift.[15] In the present work, the isomers with endo methoxy or ethoxy groups had shorter GC retention times. The methoxy derivatives had more easily interpreted spectra.

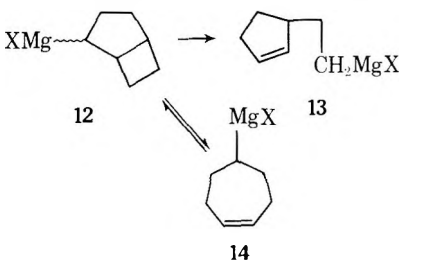
The conformation of cycloheptenes has been discussed by a number of workers.[16] Although there is some disagreement, it appears that both chair (**11a**) and boat (**11b**) forms may be reasonably accessible energetically. The boat form may undergo pseudorotation through the apparently high-

11a **11b** **11c**

er energy twist-boat (**11c**), but the chair form is more rigid. NMR spectra of the 5-substituted cycloheptenes prepared in the present work are of some interest. The C_5 proton of both the alcohol and its acetate appear as well-resolved multiplets, showing coupling to two sets of two protons, probably those cis and trans at C_4 and C_6 (apparent J = 3.8, 8.6 Hz in the alcohol; 4.0, 8.0 Hz in the acetate). However, the bromide has only an unresolved multiplet of comparable width. The difference is probably a consequence of virtual coupling to other ring hydrogens, rather than a difference in conformation; a two-proton multiplet (probably at C_4 and C_6), which appears at high field in the alcohol and acetate, is deshielded in the bromide so as to fall within the multiplet of other ring hydrogens. In the Grignard reagent, the C_5 proton is a pentuplet resulting from apparently equal coupling to four protons ($J \sim 5.5$ Hz). The difference could be attributed either to conformational difference, or to a "deceptively simple" situation. Unfortunately, the coupling patterns do not allow a clear choice among conformations. Examination of models suggests that an axial C_5 hydrogen in either the chair or boat conformation should have one large and one quite small coupling constant, while an equatorial C_5 hydrogen in either conformation should have two rather small coupling constants.

Preparation and Rearrangement of Grignard Reagents. Grignard reagents, prepared in ether or THF solution from halides **2, 3, 6,** and **9,** were heated in sealed tubes. Products of reaction were determined by hydrolysis of the reagent, followed by their separation with gas chromatography. In some instances, NMR spectra of the intact Grignard reagent provided evidence of the reaction. By analyzing products as a function of time, a measure of the rate of reaction could be obtained. Kinetics results are listed in Table I. This table also includes rough rate estimates made by analysis of only one to three samples of heated Grignard rather than the minimum of six to eight tubes used for the better kinetics runs.

The 2-Bicyclo[3.2.0]heptyl Grignard. Rearrangement of the unsubstituted 2-bicyclo[3.2.0]heptyl Grignard reagent **12** in ether solution was studied at temperatures between 80 and 115 °C (eq 4). Cleavage to the primary cyclo-

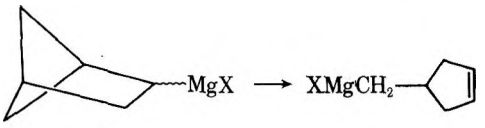


(4)

pentenylethyl Grignard **13** as the major pathway was indicated by the appearance of a high-field CH_2Mg triplet in the NMR spectrum of the heated Grignard. Gas chromatographic analysis of the hydrocarbons formed by hydrolysis showed that the secondary cycloheptenyl Grignard **14** was a minor rearrangement product (6.7% at 114.6 °C to 9.6% at

87.6 °C). At much longer heating times, it appeared that **14** was slowly converted to **13**. This was confirmed by independent preparation and rearrangement of **14**. The conversion of **14** to **13** presumably occurred via cyclization to **12**, although this intermediate did not reach sufficient concentration to allow the detection of any bicyclo[3.2.0]heptane on hydrolysis. Norbornane, resulting from minor amounts of 7-bromonorbornane present in both starting bromides, comprised a constant fraction of the hydrolysis products.

In a previous publication,[17] it was pointed out that 2-bicyclo[2.1.1]hexyl Grignard reagents **15** undergo ring cleavage reactions considerably more slowly than the monocyclic analogue **16**, despite a somewhat greater relief of ring strain



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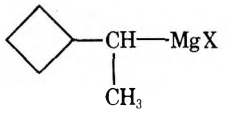
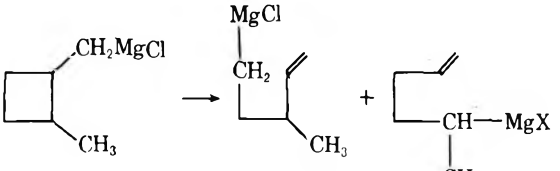


16a, X = Cl
b, X = Br

during cleavage of the bicyclic organomagnesium. The difference was attributed to the inability of the more rigid bicyclic Grignard to attain optimum transition state geometry without energetically costly distortion.

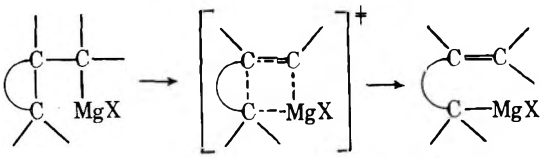
The cleavage reaction of **12** to **13** may be retarded in a similar fashion. As shown in Table I, **12** rearranges more slowly than **16b** by a factor of 0.059. A correction should be made to allow for the fact that the bicyclic Grignard has a cis 2-alkyl substituent on the cyclobutane ring. Since *cis*-**17** cleaves to **18**, with a rate about 0.3 that of cyclobutylmeth-



17 **18** **19** (5)

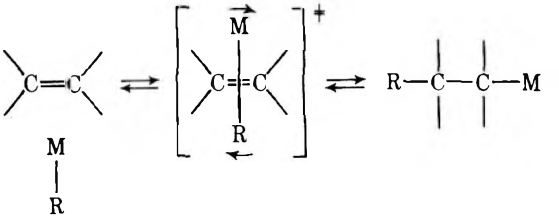
ylmagnesium chloride,[18] a corrected relative rate for the rearrangement **12** → **13** would be about 0.2. This decrease in rate is found despite a probable increase in thermodynamic driving force for the reaction (by release of ring strain). Unfortunately, heat of formation information is not available for the bicyclo[3.2.0]heptyl ring system, so this conclusion must be based on estimates of the strain energy.[19,20]

Formation of the minor cycloheptenyl Grignard product **14** in significant amount warrants comment. In terms of product stability alone, this is anticipated to be the lesser of the two products, since a secondary Grignard is about 3–5 kcal/mol less stable than a primary one,[25-27] and the strain energies of cyclopentene and cycloheptene are similar.[21] In the simpler cleavage reaction of eq 5, where the choice is also between formation of primary (**18**) and secondary (**19**) Grignards, the primary predominates by a factor of close to 100. In the absence of additional factors, then, a comparable ratio of ca. 100:1 might have been expected for **13**:**14** also. Such an additional factor may indeed exist. The most obvious model for the previously supported four-center transition state[2,3] is one in which the four atoms involved are arranged in an approximately coplanar and rectangular array:

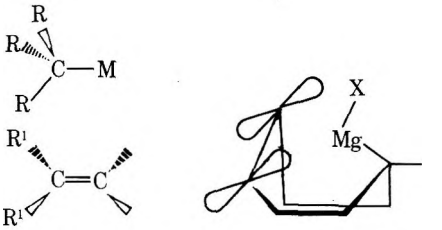


Examination of models shows that such a configuration can be attained for the cleavage to the cyclopentenylethyl Grignard **13** with minimal bond bending, though probably some increase in torsional strain. However, the distortion necessary to pass through such a transition state en route to **14** should be prohibitive. Yet, the rearrangement path to secondary Grignard (**12** → **14**) competes more favorably in the constrained bicycloheptyl Grignard than in the more flexible case of **17** → **19**. Furthermore, it appears that the absolute rates of these two rearrangements yielding secondary Grignard are similar.[28] We must therefore conclude that the reaction coordinate leading to **14** more closely resembles the ideal geometry for this reaction than the one leading to **13**, and that the "coplanar rectangular" model is a poor one for this transition state.

Additional insight into the reaction coordinate may be drawn by viewing it in the reverse direction—as an intramolecular addition. The "coplanar-rectangular" transition state corresponds to a parallel approach of the C–Mg bond to one lobe of the C=C π orbital. In an alternative reaction coordinate, the approach might be in perpendicular fashion:



A similar reaction coordinate has been proposed on other grounds by Eisch for the addition of triphenylaluminum to alkynes.[29a] This reaction path may have the additional virtue of avoiding the unfavorable steric interactions illustrated in **20**, which are present in any coplanar approach. In the present instance, we might note that a substituent in the axial 5 position of a boat cycloheptene (**21**) is held in a location over the double bond, probably ideal for a "perpendicular" approach to the addition.[29b]

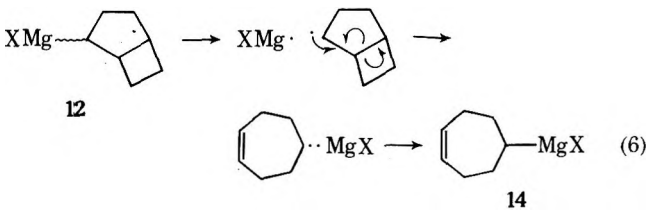


20 **21**

A reaction coordinate involving this perpendicular approach would also fit well with the notion of a π-complex intermediate in the addition. Intramolecular interaction of the metal of an organometallic with olefinic π electrons has been demonstrated for organolithium, -aluminum, and -zinc compounds,[30] and π-complex intermediates are widely considered in additions of organometallics to alkenes or alkynes.[31] Such a mechanism has been suggested for the Grignard cyclization–cleavage process, though without firm experimental support.[2-4]

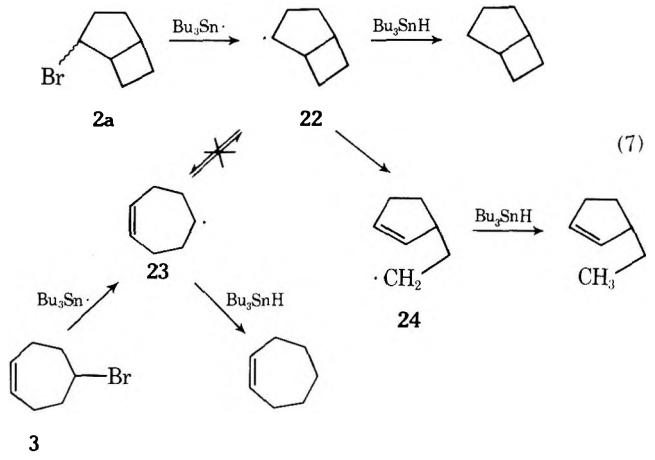
A possible alternative to the logic above is that the reaction proceeds by two concurrent mechanisms—a coplanar

four-center cleavage to the cyclopentenylethyl Grignard **13**, and a competing *radical* cleavage to the cycloheptenyl Grignard (eq 6). However, additional experiments render this



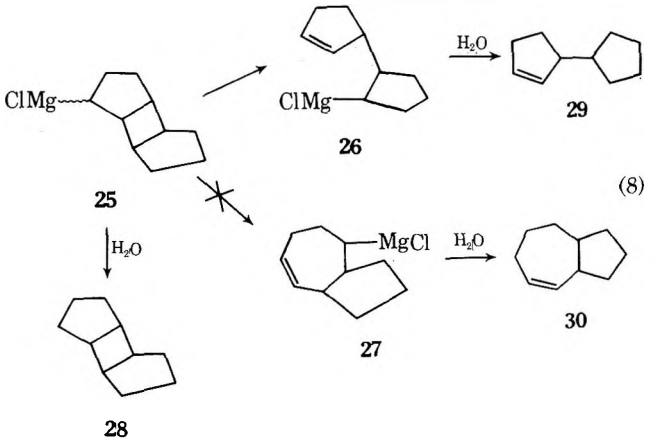
(6)

explanation untenable. Reduction of either **2a** or **3** with tri-*n*-butyltin hydride in the absence of solvent led to the corresponding hydrocarbon as essentially the only product. In 0.02 M hydride solution, reduction of excess **2a** gave sizable amounts of 3-ethylcyclopentene, resulting from partial rearrangement of the intermediate radical **22**. The absence of cycloheptene in the product, and of significant amounts of 3-ethylcyclopentene from reduction of **3**, indicate that interconversion of radicals **22** and **23** is much slower than rearrangement of **22** to **24**. Therefore, a radical mechanism cannot explain the formation of **14**.



(7)

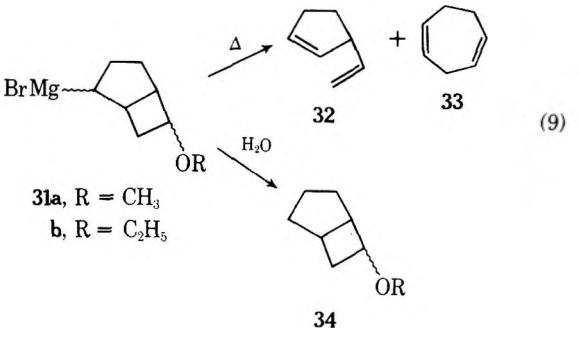
The 3-Tricyclo[5.3.0.0^{2,6}]decyl Grignard (25). With the tricyclic Grignard reagent **25**, rearrangement by either of the two available bond cleavages would produce a secondary Grignard reagent (eq 8). Since cleavage to the (secondary) cycloheptene was unexpectedly favorable in rearrangement of the bicyclic Grignard **12**, it might have been anticipated to compete even more strongly here. It was found that **25** does rearrange slowly, but that hydrolysis yielded only the hydrocarbons **28** and **29**, corresponding to unrearranged and the rearranged Grignard **26**, respectively. There was no evidence for the presence of **30**, so cleavage to **27** must be unimportant. Examination of models suggests



(8)

that the rigidity imposed by the additional fused ring may destabilize **27** relative to **26**. The conformation with a chair cycloheptene should be badly strained—the dihedral angle between bonds in the cyclopentane ring would have to be nearly 90°—and interconversion between boat conformations should also be quite hindered. It may be that the added strain is severe enough to decrease the rate of cleavage by this pathway to a very small value. Alternatively, recyclization of **27** to **25** may occur rapidly enough that the concentration of the former never reaches a significant level.

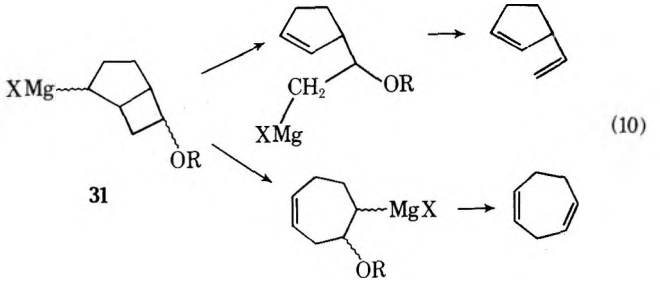
The 6-Alkoxybicyclo[3.2.0]hept-2-yl Grignard Reagents. A study of the alkoxy-substituted Grignard reagents **31** was initiated to investigate the possibility of concerted fragmentation processes, in which breaking of the C_6–alkoxy bond occurs in the same step as C_2–Mg cleavage.



(9)

Such processes would have as driving force the conversion of a magnesium alkyl to a magnesium alkoxide. Examination of models suggests that in the transition states **35** and **36** for a concerted fragmentation, twisting and puckering of the rings allows the cleaving bonds to *approach* an electronically favorable anti-coplanar orientation about each of the forming double bonds (though all *three* bonds undergoing cleavage cannot be mutually coplanar). Similarly in **37**, the two eliminations are syn and anti copolanar. Coordination between the departing magnesium and alkoxy functions would provide further assistance to cleavage, as shown in **38**. However, close approach of the ether oxygen to the magnesium requires twisting away from an anti-coplanar orientation. In transition state **39**, both eliminations would be anti, but the product would be *trans,trans*-1,4-cycloheptadiene. It is important to note that **35**–**38** are all specific to elimination of an endo alkoxy group, but that the exo epimer probably does not have a reasonable concerted pathway.

Alternatively, cleavage to yield the same products might occur in stepwise fashion, as shown in eq 10.

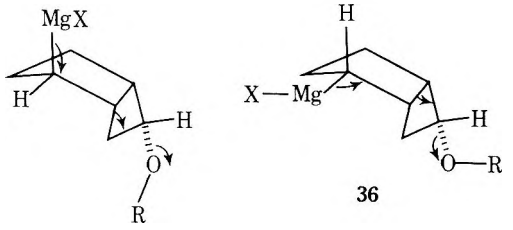


(10)

On heating, Grignard reagents **31** did cleave to yield the dienes 3-vinylcyclopentene (**32**) and 1,4-cycloheptadiene (**33**) as major and minor product, respectively. The Grignard solutions studied were mixtures of the epimers with exo and endo alkoxy groups. It was apparent, from analysis of solutions heated for different periods of time before hydrolysis, that the epimers showed quantitative differences

in their behavior. The epimer with endo alkoxy decomposed substantially more rapidly. For example, although *endo*-**31b** had rearranged nearly completely after 1 h at 80°, the *exo*-**31b** in the same solution disappeared with a half-life of 2–3 h. Compared with the cleavage rearrangement of Grignard reagent **12**, the approximate relative rates of *endo*- and *exo*-**31** were about 10^3 and 30, respectively. The products from the two epimers also differed. Product formed in the later stages of the reaction, when only *exo*-**31** was reacting, had about 15–20% of the minor cycloheptadiene product **33**. Early in the reaction it was present in smaller amounts, consistent with its formation as 5–10% of the product from *endo*-**31**. A more accurate comparison between epimers was precluded by sizable amounts of disproportionation during formation of the Grignard.

The increased cleavage rates of both epimers are consistent with the operation of an electron-withdrawing inductive effect of the alkoxy group, which stabilizes the intermediate structures in the stepwise mechanism of eq 10.[32] The greater rate with endo alkoxy could be a consequence of relief of steric repulsions present in the starting material. Alternatively, it may be evidence for the importance of concerted fragmentations such as **35–38**, which are specific



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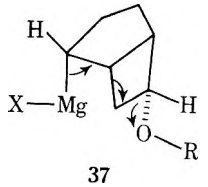

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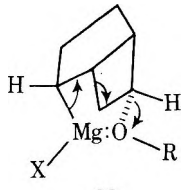

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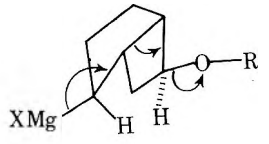

39

to this epimer. The product mixture observed may be more difficult to rationalize with the concerted mechanism. The relative amounts of cleavage to the seven-membered ring products for both exo and endo alkoxy (15–20 and 5–10%, respectively) are similar to that found in the cleavage of **12** (7–10%). It requires a rather remarkable coincidence for *endo*-**31**, reacting by two or more concerted fragmentation pathways which are specific to a single product, to yield nearly the same mixture of five- and seven-membered ring products as *exo*-**31** and **12**.

Experimental Section

Spectra were run on Varian Associates A-60, T-60, and HA-100 NMR spectrometers, and Beckman IR-5 and IR-8 ir spectrophotometers. Gas chromatography was on Varian Aerograph A-90-P chromatographs, using the following columns: A, 0.25 in. × 10 ft, 20% Carbowax 20M on Chromosorb P; B, 0.25 in. × 10 ft, 25% Ucon polar on firebrick; C, 0.25 in. × 10 ft, 20% poly-*m*-phenyl ether on Chromosorb P; D, 0.25 in. × 5 ft, Tide.

Preparation and Handling of Grignard Reagents. Grignard reagents were prepared in a flask sealed to a condenser, with a side arm above the condenser for attachment to a nitrogen source or vacuum line. The solvents used were distilled from lithium aluminum hydride under a slow stream of nitrogen and transferred by syringe. Magnesium was a sublimed grade.[34] When necessary, a small crystal of I_2 or a very small amount of methyl iodide, ethyl bromide, or ethylene chloride was used to help initiate the reaction. Reactions were run under a slight positive pressure of dry nitrogen. In instances where hydrolysis or disproportionation products were sufficiently volatile, the solvent and any volatile components were pumped to a cold trap under high vacuum, and replaced by fresh solvent. Samples of Grignard (ca. 0.5–1 ml) were sealed in ampules, and sometimes in an NMR tube. After heating, the ampules were opened in an inert atmosphere "glove bag", and either hydrolyzed immediately or fitted to an adapter which allowed volatiles to be pumped to a trap before hydrolysis. Hydrocarbon products were analyzed by gas chromatography, on the assumption of equal sensitivity of isomeric hydrocarbons. Rearrangement rates were determined from a plot of log ([unrearranged]/[unrearranged] + [rearranged]) vs. time.

2-Halobicyclo[3.2.0]heptanes (2). *exo*-2-Bicyclo[3.2.0]heptanol was prepared as reported by Winstein and Stafford:[5] bp 85–86 °C (20 mm); n^{25}D 1.4850; NMR (CCl_4) δ 3.88 (d, 2, J = 3.0 Hz), 3.62 (s, 1, OH), and 1.0–3.0 ppm (m, 10). Reaction of 1.0 g (8.9 mmol) of the alcohol with thionyl chloride (1.06 g, 8.9 mmol) and pyridine (0.70 g, 8.9 mmol) yielded 0.30 g (26%) of product: bp 60 °C (20 mm); n^{24}D 1.4857; NMR (CCl_4) δ 1.0–3.0 (m, 10), 3.89 (s, broad, ca. ⅔ H), and 4.12 ppm (d, ca. ⅓ H, J = 3.7 Hz). This mixture was not studied further.

To a stirred solution of the alcohol (10.0 g, 0.089 mol) and triphenylphosphine (24.5 g, 0.0935 mol) in dry dimethylformamide (50 ml) at 50–57 °C, bromine (14.5 g, 0.089 mol) was added over a period of 45 min. After an additional 1 h of heating at this temperature, the mixture was distilled under vacuum (up to 80 °C at 1 mm). The distillate was diluted with 50 ml of saturated aqueous sodium chloride and extracted with petroleum ether. The extract was washed with aqueous sodium chloride solution, distilled twice, and chromatographed on alumina to yield 4.5 g (30%) of product: bp 69° (10 mm); n^{27}D 1.5092; NMR (neat) δ 3.9–4.45 (m, 1, CHBr) and 1.0–3.2 ppm (m, 10).

Anal. Calcd for $C_7H_{11}Br$: C, 48.02; H, 6.33. Found: C, 48.29; H, 6.43.

Gas chromatography on column A showed the presence of three components in relative amounts (in order of increasing elution time) of 12.5, 21.5, and 66%.

Grignard Reagent from 2-Bromobicyclo[3.2.0]heptane. Grignard reagents were prepared from the bromide and an excess of sublimed magnesium in ether or tetrahydrofuran solution.

After completion of the reaction, the solvent and any volatile materials present were pumped to a cold trap (at ca. 5 μ pressure), and fresh solvent was added. Gas chromatographic examination (column B) of either the volatiles from the Grignard preparation or the product of hydrolysis of the Grignard (with cold 3 N HCl) showed two hydrocarbons. The first of these, present to the extent of 10% in the volatiles from the Grignard preparation and 13–14% in the hydrolysis product, had retention time and infrared and NMR spectra identical with those of authentic norbornane. The major component of the Grignard hydrolysis was identified as bicyclo[3.2.0]heptane on the following basis: (a) mode of formation, as major hydrolysis product from the starting halide; (b) ir spectrum, with major peaks coinciding in position with those in an authentic dilute solution spectrum kindly furnished to us by Professor W. G. Dauben; (c) NMR spectrum, which had complex absorption from δ 1.0 to 2.4 ppm and a broadened singlet at 2.75 ppm in a ratio of 10:2, but no olefinic proton absorption. The NMR spectrum of the Grignard in THF (ca. 0.8 M) had a broad, ill-defined multiplet from about δ 0.1 to −0.6 ppm, and no olefinic absorption.

When the Grignard solutions were heated for a number of hours in sealed tubes in the vicinity of 100 °C, changes occurred both in the NMR spectrum and in the hydrolysis products. In the NMR, there appeared a prominent triplet at δ −0.5 ppm (J = 8.5 Hz, CH_2Mg) and olefinic absorption at 5.66 ppm (apparent AB quartet, $J_{AB} \simeq$ 5.5 Hz, with probable further triplet splitting of ca. 2 Hz). Hydrolysis yielded two new components, formed initially in a ratio of about 10:1. The first of these was identified as 3-ethylcyclopentene: NMR (CCl_4) δ 0.91 (t, 3, J = 7 Hz, CH_3), 1.0–2.8 (m, 7), and 5.63 ppm (s, 2, olefinic); ir identical with published spectrum.[35] The second (minor) component was cycloheptene: NMR (CCl_4) δ 1.65 (m, 6), 2.13 (m, 4, allylic), and 5.72 ppm (apparent triplet, 2, J = 3.5 Hz, olefinic) and identical with an authentic sample; ir identical with published spectrum[36] and authentic sam-

ple. At long heating time, the cycloheptene in the Grignard hydrolysis product decreased relative to the 3-ethylcyclopentene.

At least two minor components having retention times similar to bicyclo[3.2.0]heptane were detected, but not identified. First, the NMR spectrum of the bicyclo[3.2.0]heptane in the volatiles pumped from the Grignard preparation indicated the presence of unsaturation (δ 5.78 ppm, s). Integration of the spectrum would be consistent with an approximately 1:1 mixture of bicyclo[3.2.0]heptane and bicyclo[3.2.0]hept-2-ene. Second, at long heating times, the GC peak corresponding in retention time to bicyclo[3.2.0]heptane remained constant at about 5% of the total product. Unsaturation was indicated by NMR (δ 5.78 and 4.71 ppm) and infrared spectra (3060 and 802 cm^{-1}). A saturated component (NMR singlets at δ 0.99 and 1.20 ppm) also appeared to be present. The olefinic NMR signals were not present in the hydrolysis product of the unheated Grignard reagent.

In determining the kinetics of the rearrangement, the concentration of unrearranged hydrocarbon was decreased to allow for the 5% of nonrearranging material. The total rate of disappearance of starting material was determined, and apportioned between the two rearrangement paths according to the average ratio of ethylcyclopentene to cycloheptene.

5-Bromocycloheptene. 4-Cycloheptenol was prepared by the method of Cope:[6] bp 68.5–70.7 °C (8 mm) [lit.[6] bp 83–84 °C (11 mm)]; NMR (CCl_4) δ 1.46 (m, 2), 1.7–2.5 (m, 6), 3.73 (triplet of triplets, 1, J = 3.8, 8.6 Hz, CHOH), 4.30 (s, 1, OH), 5.69 ppm (m, 2, olefinic).

Phosphorus tribromide (7.08 g, 26 mmol) was added dropwise to a mixture of 4-cycloheptenol (7.9 g, 69 mmol) and pyridine (1.45 g, 18 mmol) in 15 ml of anhydrous ether cooled to 0 °C. The mixture was allowed to warm to room temperature and stand overnight. The ether was distilled at atmospheric pressure, and then the residue was slowly heated under vacuum (~8 mm) to a maximum temperature of 105 °C. Product distilled to a receiver. Redistillation yielded 5.8 g: bp 62–64 °C (8 mm); NMR (CCl_4) δ 1.7–2.5 (m, 8), 4.39 (s, b, 1, CHBr), 5.76 ppm (m, 2, olefinic). Gas chromatography (column B) showed the presence of a minor component (ca. 10%) eluted just ahead of the major bromide.

Anal. Calcd for $C_7H_{11}Br$: C, 48.02; H, 6.33. Found: C, 47.85; H, 6.28.

Grignard Reagent from 5-Bromocycloheptene. A Grignard reagent was prepared from 5-bromocycloheptene and magnesium in dried ether. Hydrolysis of the Grignard reagent yielded a mixture of hydrocarbons consisting principally of cycloheptene (86%) and norbornane (9%), as shown by GC analysis (column B). Two minor components of longer retention time, both unsaturated, were present. The solvent pumped from the Grignard preparation had the same components, with the norbornane and cycloheptene comprising about 50% of the total. The ir and NMR spectra of the major longer retention time component were identical with those of 1,4-cycloheptadiene (see below).

An NMR spectrum of the Grignard solution in ether showed olefinic absorption at δ 5.7 ppm as an unsymmetrical complex multiplet, about 15 Hz wide. The CHMg resonance was obscured by the solvent side bands in ether, but appeared at δ 0.5 ppm in THF solution. It was an apparent pentuplet, with J = 5.5 Hz. A weak broad doublet absorption at δ −0.4 ppm was not identified.

The Grignard solution in ether was heated for 92 h at 130 °C. Volatiles were removed under vacuum and the residual Grignard was hydrolyzed. As before, the product contained cycloheptene and norbornane, but the major component was identified as 3-ethylcyclopentene. About 72% of the cycloheptenyl component had undergone rearrangement. The volatiles pumped from the Grignard before hydrolysis contained the same components as previously, with cycloheptene comprising the major portion. The norbornane appeared to have remained as a constant 8–10% of the total products. A sample heated for 120 h at 110 °C showed a smaller fraction of rearrangement (6–7%).

The NMR spectrum of the heated Grignard reagent showed additional rather ill-defined olefinic absorption at δ 5.45–5.65, and a sharp singlet at 5.33 ppm attributed to ethylene formed by attack of Grignard on the ether solvent. A high-field CH_2Mg triplet appeared at −0.50 ppm, with J = 8.5 Hz.

6-Alkoxybicyclo[3.2.0]heptan-2-ones (4a and 4b). An excess of methyl vinyl ether (3–4 ml) was condensed into Pyrex ampules of 1-cm diameter. 2-Cyclopenten-1-one (2 g) was added to each, and the ampules were sealed under vacuum. The ampules were exposed for 24 h to the output of a Hanovia 450-W mercury arc lamp, while immersed in a bath of water at about 10 °C. After irradiation, the ampules were opened and combined, and the mixture distilled to yield 71% of **4a:** bp 216, 110–112 °C (20 mm); ir (CCl_4) 1748, 1124 cm^{-1}; NMR (CCl_4) δ 4.1–3.4 (m, 1, CHO), 3.17 (s, 3, OCH_3), and 3.1–1.4 ppm (m, 8). Gas chromatography (columns C and D) showed that the product was a mixture of two incompletely separated components present in roughly equal amount.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57, H, 8.57. Found: C, 68.28; H, 8.49.

A similar reaction of cyclopentenone (25 g, 0.30 ml) and ethyl vinyl ether (50 ml) yielded a mixture of **4b:** bp 62–65 °C (1 mm); ir (CCl_4) 1742, 1120 cm^{-1}; NMR (CCl_4) δ 4.25–3.6 (m, 1, CHO), 3.32 (q, 2, J = 7 Hz, CH_2O), 3.1–1.35 (m, 8), 1.4 ppm (t, 3, J = 7 Hz, CH_3). Gas chromatography (column C) again showed a mixture of two partially separated components in approximately a 1:1 ratio.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 70.02; H, 8.83.

6-Alkoxybicyclo[3.2.0]heptanes (34a and 34b). A mixture of methoxy ketone **4a** (2.52 g, 0.018 mol), 85% hydrazine hydrate (20 ml), and diethylene glycol (20 ml) was heated at reflux for 45 min. The mixture was cooled, potassium hydroxide (6.7 g, 0.12 mol) was added, and the mixture was distilled slowly up to a pot temperature of 190 °C. The distillate was extracted with pentane, dried (Na_2SO_4), and distilled to yield 1.15 g (45%) of **34a,** ir (CCl_4) 1123 cm^{-1}. The product was a mixture of two components present in equal amount, which were separated by preparative GC (column C, in order of increasing retention time): (1) endo methoxy, NMR (CCl_4) δ 4.1–3.3 (m, 1, CHO), 3.10 (s, 3, OCH_3), and 3.0–1.25 (m, 10); and (2) exo methoxy, NMR (CCl_4) δ 3.6–3.15 (m, 1, CHO), 3.10 (s, 3, OCH_3), 2.6 (s, b, 2, bridgehead), and 2.35–1.15 ppm (m, 8).

Anal. Calcd for $C_8H_{14}O$: C, 76.14, H, 11.18. Found: C, 76.23; H, 10.95.

A similar mixture was produced by reaction of bromide **6a** (1 g) with an equimolar quantity of tri-*n*-butyltin hydride in refluxing benzene. Reduction of **6a** (1 g) by addition as a solution in 2 ml of ethanol to 0.25 g of molten sodium yielded a mixture of products shown by NMR to contain some unsaturation. On GC column D, the product was separated into two portions. The first of these (18%) had ir (CCl_4) 1640 (C=C) and 1078 cm^{-1}; NMR (CCl_4) δ 5.7 (b, 2, =CH), 3.75–3.25 (m, 1, CHO), 3.15 (s, 3.0 CH_3), and 3.1–1.9 ppm (m, 6), and was tentatively identified as *endo*-6-methoxybicyclo[3.2.0]hept-2-ene. The second appeared to contain mostly the expected saturated reduction product, along with about 15–20% of an olefinic component.

Wolff–Kishner reduction of the ethoxy ketone **4b** was carried out in similar fashion: ir (CCl_4) 1133 and 1108 cm^{-1}. The components were separated by preparative gas chromatography on column C: (1) endo ethoxy, NMR (CCl_4) δ 3.82 (q, b, 1, J = 7.5 Hz, CHO), 3.27 (q, 2, J = 6.8 Hz, CH_2O), 3.0–1.3 (m, 10), and 1.11 ppm (t, 3, J = 6.8 Hz, CH_3); (2) exo ethoxy, NMR (CCl_4) δ 3.3 (q, superimposed on an unresolved multiplet, 3, $J_{quartet}$ = 6.8 Hz, CHO and CH_2O), 2.6 (s, b, 2, bridgehead), 2.4–1.3 (m, 8), 1.11 (t, 3, J = 6.8, CH_3).

6-Alkoxybicyclo[3.2.0]-heptan-*endo*-2-ols (5a and 5b). A suspension of methoxy ketone **4a** (10.9 g, 0.072 mol) in 50 ml of 2 N sodium hydroxide was added in portions to a solution of sodium borohydride (2.0 g, 0.072 mol) in 15 ml of 2 N sodium hydroxide. The mixture was stirred and maintained at 35–40 °C by cooling during the addition, then heated gradually to 90 °C over 2 h and maintained at that temperature for 1.5 h. Anhydrous potassium carbonate (9.6 g) was added, the organic layer was separated, and the aqueous phase was extracted with ether. The organic solutions were dried (Na_2SO_4) and distilled to yield 7.5 g (68.5%) of **5a:** bp 127–130° (20 mm); ir (CCl_4) 3457, 1207, 1120, and 1072 cm^{-1}. The product was found by GC to consist of two components which were preparatively separated (column D) for spectroscopic characterization: (1) endo methoxy, NMR (CCl_4) δ 4.1–3.4 (m, 3, OH and CHO), 3.13 (s, 3, OCH_3), and 2.9–1.2 ppm (m, 8); (2) exo methoxy, NMR (CCl_4) δ 4.2–3.7 (m, 2, OH and C_2HO), 3.25 (m, 1, C_6HO), 3.13 (s, 3, OCH_3), 2.5 (s, b, 2, bridgehead), and 2.5–1.3 (m, 6).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.86. Found: C, 67.57; H, 9.88.

The ethoxy ketone **4b** was reduced to **5b** by addition of sodium borohydride (2.5 g, 0.066 mol) in small portions to a solution of ketone (20.9 g, 0.135 mol) in 100 ml of absolute ethanol. The mixture was refluxed for 3 h, 100 g of 25% aqueous sodium hydroxide was added, reflux was continued for 1 h, and 100 ml of water was added. The product was extracted into ether, washed, dried, and distilled to yield 18.7 g (90%): bp 77–81 °C (1 mm); ir (CCl_4) 3454, 1192, 1120, and 1070 cm^{-1}. The mixture had NMR absorption for the ethoxy group at 3.28 and 1.13 ppm (J = 7 Hz) and multiplet absorption in the region 4.4–3.5 ppm attributable to the CHO pro-

tons. Partial resolution could be obtained by gas chromatography (column C), but spectra of the separated fractions were relatively uninformative.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 69.15; H, 10.49.

***exo*-2-Bromo-6-alkoxybicyclo[3.2.0]heptanes (6a and 6b).** Bromine (7.2 g, 0.045 mol) was added dropwise over a period of 30 min to a stirred solution of **5a** (6.4 g, 0.045 mol) and triphenylphosphine (11.8 g, 0.045 mol) in 80 ml of dry dimethylformamide, maintained at 55 °C. After 2.5 h of additional heating at 55 °C, the reaction mixture was distilled, up to a pot temperature of 90 °C (1 mm). The distillate was extracted with 30–60 °C petroleum ether. The extract was washed (aqueous NaCl), dried ($CaCl_2$), and distilled to give a 61% yield of **6a**: bp 69–70 °C (1 mm); ir (CCl_4) 1207, 1120, and 1072 cm^{-1}. Analysis by gas chromatography (columns C and D) showed the presence of two components, which were preparatively separated for spectroscopic characterization: (1) endo methoxy, NMR (CCl_4) δ 4.25 (d, 1, $J \sim 3$ Hz, CHBr), 4.0–3.5 (m, 1, CHO), 3.14 (s, 3, OCH_3), and 3.1–1.0 ppm (m, 8); (2) exo methoxy, NMR (CCl_4) δ 4.25 (d, 1, $J \sim 3$ Hz, CHBr), 3.3 (m, 1, CHO), 3.14 (s, 3, OCH_3), and 3.1–1.0 ppm (m, 8).

Anal. Calcd for $C_8H_{13}BrO$: C, 46.85; H, 6.34. Found: C, 46.88; H, 6.45.

In analogous fashion, **5b** was converted to **6b** in 53% yield: bp 90° (1 mm); ir (CCl_4) 2999, 1291, 1229, 1199, 1133, 1119, 898, 734, and 711 cm^{-1}. The NMR spectrum had a total of four hydrogens at low field (4.4–3.0 ppm), including a one-proton doublet at 4.20 ppm ($J \sim 3$ Hz, CHBr), a two-proton quartet at 3.27 ppm ($J = 7$ Hz, CH_2O), and additional absorption totaling about one hydrogen, partially obscured by the ethoxy quartet, and partially appearing as an apparent quartet at 3.84 ppm ($J \sim 7$ Hz). Along with complex absorption from 3.0 to 1.3 ppm, the methyl triplet appeared at 1.12 ppm ($J = 7$ Hz). Gas chromatography (column C) indicated a mixture of two components, present in approximately equal amounts.

Grignard Reagents from 6a and 6b. Grignard reagents were prepared from 0.5–2-g samples of **6a** or **6b** and an excess of sublimed magnesium in ether, following the general procedure. Concentrations were determined by acid titration and, in some cases, by complexiometric titration for magnesium. In either case, hydrolysis yielded a similar mixture which was partially resolved by gas chromatography (columns C and D). The major GC fraction was a broadened peak which included both exo and endo isomers of the appropriate 6-alkoxybicyclo[3.2.0]heptane, along with small amounts of an unsaturated component tentatively assigned as the exo-6-alkoxybicyclo[3.2.0]hept-2-ene. The probable endo isomer of the latter was eluted shortly before the major peak. This portion of the product closely resembled the product of sodium–ethanol reduction of **6a** (see above). The unsaturated components, which are presumed to have originated in a side reaction during Grignard reagent formation, comprised about 25–30% of the total product. On heating for a period of hours in the vicinity of 80 °C two new components appeared, which increased with time at the expense of the major fraction. These were identified by comparison of ir and NMR spectra and GC retention times with authentic samples of 3-vinylcyclopentene (**32**) and 1,4-cycloheptadiene (**33**) (in order of retention time). In some cases, the Grignard reagent appeared to have significant amounts of the former before heating. They were formed in a ratio of 5 to 10:1. In addition, both Grignard reagents contained a small amount (<1%) of an unidentified component eluted between **14** and **15**, which appeared saturated from its NMR spectrum, and which did not vary with heating time.

3-Vinylcyclopentene was prepared by the reaction of a Grignard reagent from 2.0 g (0.019 mol) of vinyl bromide in THF with 2.0 g (0.02 mol) of 3-chlorocyclopentene. The reaction mixture was hydrolyzed, dried (Na_2SO_4), and distilled to yield 0.8 g (40%) of product: bp 91–93 °C (lit.[37] bp 93 °C); ir (CCl_4) 3100 and 1620 cm^{-1} (C=C); NMR (CCl_4) δ 5.45–6.20 (m, 3, =CH), 4.70–5.20 (m, 2, $=CH_2$), 3.2 (m, 1), and 2.5–1.2 ppm (m, 4).

1,4-Cycloheptadiene was prepared by the method of Doering and Roth.[38] Components separated by GC and characterized by NMR were cycloheptene, 1,4-cycloheptadiene, and unreacted 1,3,5-cycloheptatriene. The diene had NMR (CCl_4) δ 5.8 (m, 4, olefinic), 3.0 (m, 2, doubly allylic), and 2.4 (m, 4, allylic).

Tricyclo[5.3.0.0^{2,6}]decan-3-ol (**8**) was prepared by addition of an ether solution of tricyclo[5.3.0.0^{2,6}]decan-3-one[7] (**7**, 5 g, 33 mmol) to lithium aluminum hydride (0.63 g, 16.6 mmol) in ether. Excess hydride was decomposed with ethyl acetate followed by water. The product was obtained in 80% yield by evaporation of the solvent and recrystallization from benzene and petroleum ether: mp 67–70 °C; NMR (CCl_4) δ 4.08 (broadened q, 1, $J \sim 7$ Hz, CHOH), 3.25 (s, 1, OH), 2.55 (broadened s, 1, bridgehead), and 2.2–1.3 ppm (m, 13); (pyridine) δ 5.57 (s, 1, OH), 4.32 (q, 1, $J = 7.5$ Hz, CHOH), 2.87 (broadened s, 1, bridgehead), and 2.3–1.3 ppm (m, 13).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.72; H, 10.66.

3-Chlorotricyclo[5.3.0.0^{2,6}]decane (9). To 5 g (33 mmol) of **8** and 2.60 g (33 mmol) of pyridine cooled to 0 °C, 4.3 g (36 mmol) of thionyl chloride was added dropwise. The temperature was raised over 2 h to about 95 °C, and maintained at that temperature for another 2 h. The reaction mixture was extracted with petroleum ether. The solvent was evaporated and the product distilled to yield 75% of product: bp 64–70 °C (0.45 mm); NMR (CCl_4) δ 4.15 (d, 1, $J = 3.2$ Hz, CHCl), 2.3–1.4 (m, 14).

Anal. Calcd for $C_{10}H_{15}Cl$: C, 70.36; H, 8.85. Found: C, 70.55; H, 9.18.

Tricyclo[5.3.0.0^{2,6}]decane (28). A mixture of 3.25 g of **7**, 15 ml of diethylene glycol, and 15 ml of hydrazine hydrate was refluxed for 15 min. Potassium hydroxide (5 g) was added, and product was distilled from the reaction mixture. The product was taken up in petroleum ether, dried, and distilled, bp 61 °C (25 mm) [lit.[39] bp 52–53 °C (10 mm)].

Grignard Reagent from 3-Chlorotricyclo[5.3.0.0^{2,6}]decane. A Grignard reagent was prepared from 1 g of the chloride and 0.172 g of sublimed magnesium in 5 ml of dry ether. Part of the solution was hydrolyzed. Gas chromatography (column B) showed two products in a ratio of 3.5:1. The first of these had GC retention time, ir, and NMR spectra identical with those of authentic tricyclo[5.3.0.0^{2,5}]decane. The minor component had retention time, ir, and NMR spectra identical with those of authentic 3-cyclopentylcyclopentene (see below). A Grignard reagent prepared in THF yielded much less of the latter.

The solution was heated for 540 h at 110 °C and hydrolyzed. The same two components were present, as shown by spectra of isolated samples. The ratio was now 1:4.

3-Cyclopentylcyclopentene was prepared by reaction of 3-chlorocyclopentene with cyclopentylmagnesium chloride.[40] Gas chromatography indicated a major component (ca. 80–85% of the total) and several minor components: bp 59–65 °C (10 mm) [lit.[40] bp 63 °C (9 mm)]; NMR (CCl_4) δ 5.9 (s, 2, olefinic) and 2.4–1.0 ppm (m, 14).

Reaction of 2a and 3 with Tri-*n*-butyltin Hydride. A solution was prepared containing tri-*n*-butyltin hydride (0.020 M) in *n*-decane which had been deoxygenated by passage of a stream of nitrogen. A 5-ml portion of this solution was heated to 80 °C with a trace of azobisisobutyronitrile, and 0.060 g (3.4×10^{-4} mol) of **2a** was added. The solution was heated for 1 h, and analyzed by gas chromatography (column B). The major hydrocarbon products, identified by GC retention times, were 3-ethylcyclopentene (29%) and bicyclo[3.2.0]heptane (61%). Minor amounts of norbornane and an unknown component were present. Cycloheptene was not detected (<1%). A reaction carried out in the absence of solvent gave only bicyclo[3.2.0]heptane. The total yield of hydrocarbon products was 50%.

A similar reaction with **3** led mainly to cycloheptene (78%) and several minor components, in a total yield of about 61%. Maximum amounts of 3-ethylcyclopentene, norbornane, and bicyclo[3.2.0]heptane, based upon the areas of GC peaks of similar retention time, were 2, 4.5, and 4.5%, respectively. It is possible that some of these may have resulted from reduction of the corresponding bromide present as an impurity in **3**.

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Registry No.—**1**, 41398-40-7; *exo*-**2a**, 57761-89-4; *endo*-**2a**, 57794-33-9; *exo*-**2b**, 57761-90-7; **3**, 54484-64-9; *endo*-**4a**, 57761-91-8; *exo*-**4a**, 57794-34-0; *endo*-**4b**, 57761-92-9; *exo*-**4b**, 57794-35-1; *endo*-**5a**, 57761-93-0; *exo*-**5a**, 57794-36-2; *endo*-**5b**, 57761-94-1; *exo*-**5b**, 57794-37-3; *endo*-**6a**, 57761-95-2; *exo*-**6a**, 57794-38-4; *endo*-**6b**, 57761-96-3; *exo*-**6b**, 57794-39-5; **7**, 57794-40-8; **8**, 57761-97-4; **9**, 57761-98-5; **28**, 5650-12-4; **29**, 2690-17-7; **33**, 7161-35-5;

endo-**34a**, 54594-95-5; *exo*-**34a**, 54561-40-9; *endo*-**34b**, 57761-99-6; *exo*-**34b**, 57794-41-9; 7-chloronorbornane, 765-80-0; 7-bromonorbornane, 13237-88-2; 4-cycloheptenol, 6925-17-3; 2-cyclopenten-1-one, 930-30-3; methyl vinyl ether, 107-25-5; ethyl vinyl ether, 109-92-2; *endo*-6-methoxybicyclo[3.2.0]hept-2-ene, 54594-94-4; 3-vinylcyclopentene, 26727-45-7; vinyl bromide, 593-60-2; 3-chlorocyclopentene, 96-40-2; (1-chloroethyl)cyclobutane, 57762-00-2; (1-bromoethyl)cyclobutane, 20826-75-9.

References and Notes

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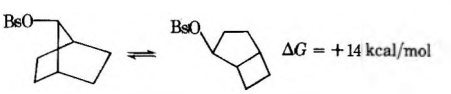
(19) The ring strain might be approximated by the sum of strain energies of the component rings. Since the strain energy of the cyclopentene ring of the product is slightly less than that of cyclopentane,[21] the cleavage of **12** would be slightly more exothermic than that of **16**.

(20) The stabilities of the [3.2.0] and [2.2.1] systems have been compared from solvolysis-derived data:[22]



Greater flexibility and the existence of enantiomers in the [3.2.0] system should combine to give it more entropy. Ignoring any other steric interactions of the brosylate group, the ring strain of the [3.2.0] system should then be *at least* 14 kcal/mol greater than the 18.5 kcal of strain of norbornane.[23] Various estimates of the additional entropy[24] suggest that the ring strain is probably 33.5–35 kcal/mol. Taken with the strain of the cyclopentene ring in the product (5.9 kcal/mol),[21] the relief of strain should be in the range of 27.5–29 kcal. In the cleavage of **16**, relief of the ring strain of cyclobutane (26.2 kcal)[21] provides the driving force.

(21) Strain energies are taken as equivalent to empirical ring corrections to heat of formation estimates, as tabulated by S. W. Benson, F. R. Cruickshank, D. M. Golden, R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).

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(24) H. E. O'Neal and S. W. Benson, *J. Chem. Eng. Data*, **15**, 266 (1970).

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(28) The rearrangement of **17**[18] has a rate relative to cyclobutylmethyl chloride of 0.3 in THF solution at 60 °C. Approximately 1% of the rearrangement leads to **19**, so the relative rate of **17** → **19** is about 3×10^{-3}. From Table I, the rate of **12** → **14** is approximately 5×10^{-3} relative to **16b** in ether solution. Since the rates of cyclobutylmethyl chloride and **16a** are the same within a factor of 2, the rates of **12** → **14** and **17** → **19** must be quite similar.

(29) (a) J. J. Eisch and R. Amtmann, *J. Org. Chem.*, **37**, 3410 (1972). (b) A referee has noted that the planar rectangular, four-center process should be disallowed on symmetry grounds. This question is discussed elsewhere,[2] and it has been pointed out that use of an additional electrophilic metal orbital removes such restrictions. Orbital symmetry constraints on the perpendicular transition state are similar to the coplanar, unless the addition is antarafacial with respect to the double bond, or occurs with inversion at one end of the adding single bond.

(30) J. B. Smart, R. Hogan, P. A. Scherr, M. T. Emerson, and J. P. Oliver, *J. Organomet. Chem.*, **64**, 1 (1974); G. Hata, *Chem. Commun.*, 7 (1968); J. St. Denis, J. P. Oliver, T. W. Dolzine, and J. B. Smart, *J. Organomet. Chem.*, **71**, 315 (1974).

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(32) The magnitude of the inductive effect might be considered in the context of the Taft σ^* correlation.[33] If σ^* for β-OR is taken as +0.52 (equal to that for CH_2OCH_3 vs. CH_3), a rate increase of 30 corresponds to $\rho^* \sim +2.8$. This value is slightly smaller in absolute magnitude than those observed in most acid dissociation equilibria (2.6–4.3), or in some carbonium ion forming reactions (~−3.5). Since the Grignard cleavage reaction leads to formation of a polar C–Mg bond rather than a carbanion, a reduced substituent effect might be expected. It is possible that the nonpolar ether solvent may significantly influence the magnitude of ρ^*.

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Homogeneous Catalyzed Reduction of Nitro Compounds. IV. Selective and Sequential Hydrogenation of Nitroaromatics

J. F. Knifton

Beacon Research Laboratories, Texaco Inc., Beacon, New York 12508

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Dichlorotris(triphenylphosphine)ruthenium(II) and related iron and ruthenium complexes have been found to catalyze the selective homogeneous hydrogenation of nitroaryls to amines. Certain of the ruthenium complexes, exemplified by $RuCl_2(PPh_3)_3$, are highly specific; dinitroaromatics may be reduced to the intermediate nitro amines in good yields, and in the presence of a second mononitroaromatic component, nitro amine synthesis may be carried out to the substantial exclusion of mononitroaromatic hydrogenation and diamine formation. Sequential hydrogenation has been demonstrated also for certain alkylated nitroaromatics, including mixtures of nitroxylene isomers, and nitropolyaromatics in the presence of nitromonoaromatics. Other functional groups such as halogen, hydroxide, alkoxide, ester, and nitrile may also be present without suffering transformation during $C-NO_2$ hydrogenation. Possible mechanisms of this multistep homogeneous reduction are discussed in relation to the observed kinetics, and the scope of the sequential hydrogenation technique as it is affected by both the electronic and steric properties of the substrates and catalysts.

Although a variety of heterogeneous catalysts already exist for the catalytic hydrogenation of nitroaromatic substrates (e.g., Adams' catalyst, Raney nickel, and copper chromite[1]), the purpose of this work was to develop novel homogeneous hydrogenation catalysts possessing unique selectivity properties not found in their heterogeneous counterparts. The intrinsic high degree of selectivity characteristic of homogeneous catalysts is now well recognized,[2,3] but this aspect of homogeneous $C-NO_2$ hydrogenation has, for the most part, been overlooked.[4] We have described in a previous paper the application of dichlorotris(triphenylphosphine)ruthenium(II), and related complexes, to the hydrogenation of nitroparaffins to secondary alkyl primary amines.[5] An improved performance for this complex is reported here for the hydrogenation of nitroaromatics (eq 1).[6]

$$PhNO_2 + 3H_2 \rightarrow PhNH_2 + 2H_2O \quad (1)$$

Selective reduction of a variety of nitroaromatic substrates has been carried out at $PhNO_2$/Ru mole ratios of 200 or more, in neutral, basic, and acidic media, at ambient temperatures or above, and superatmospheric H_2 pressures. Other catalyst precursors include $[RuCl_2(CO)_3]_2$, $RuCl_2(CO)_2(PPh_3)_2$, and related complexes of ruthenium and iron. The uniqueness of certain of the ruthenium complexes lies not only in their ability to selectively hydrogenate variously substituted mono- and dinitroaromatics, but also their ability to sequentially reduce mixtures of two or more classes of nitroaromatic, to the substantial exclusion of other fractions.[7] Sequential hydrogenation is exemplified herein for mixtures of alkylated nitroaromatics, mixtures of nitrobinuclear and mononuclear aromatics, and mixtures of mononitroaromatics with dinitroaromatics.

Experimental Section

Materials. Hydrogen (prepurified grade) and deuterium (technical grade) were purchased from the Matheson Co.; dichlorotris(triphenylphosphine)ruthenium(II), dichlorotricarbonylruthenium(II) dimer, ruthenium acetylacetonate, iron pentacarbonyl, and iron naphthenate were also commercial samples; tricarbonylbis(triphenylphosphine)iron,[8] tricarbonylbis(triphenylarsine)iron,[8] and dichloro(dicarbonyl)bis(triphenylphosphine)ruthenium(II)[9] were prepared by the published methods. Nitrobenzene was redistilled prior to use; all other nitroaromatics were commercial samples and were used as received.

Synthesis Procedure. All syntheses of aromatic amines were carried out under superatmospheric pressures of H_2 in a glass-lined "autoclave" pressure reactor of 300-ml capacity, fitted with mechanical stirring, and linked to a temperature controller and recorder and a pressure gauge.

A known weight of iron or ruthenium complex (0.1–1 mmol) is dissolved, with stirring, in a 100-ml sample of predried N_2-saturated equivolume benzene–ethanol mixture containing 10–100 mmol of nitroaromatic, alkali-metal hydroxide is added as required, and the mixture transferred to the pressure reactor. Hydrogenation is carried out under a constant pressure of hydrogen (20–100 atm), while heating to temperature (25–150 °C) for 1–6 h. On cooling, the product liquid is concentrated under reduced pressure, and the amine product isolated by ether extraction. The aromatic amines are identified by ir, NMR, and by comparison with authentic samples. A typical synthesis of 2,6-xylidine from 2-nitro-*m*-xylene, catalyzed by $RuCl_2(PPh_3)_3$, gave the following results: material balance, 101%, conversion of 2-nitro-*m*-xylene, 98%, yield of isolated 2,6-xylidine, 81 mol %. Anal. Calcd for $C_6H_3(CH_3)_2NH_2$: C, 79.3; H, 9.15; N, 11.55. Found: C, 79.0; H, 9.4; N, 11.4.

Sequential Hydrogenation. Sequential hydrogenation experiments were also carried out in the 300-ml "autoclave" pressure reactor described above. Dichlorotris(triphenylphosphine)ruthenium(II) (0.1–0.5 mmol) is dissolved in a predried, N_2-saturated mixture of benzene (45 ml) and ethanol (50 ml), and the red solution heated to temperature under a moderate pressure of hydrogen (5–10 atm) in the pressure reactor. A mixture of two or more nitroaromatics (10–100 mmol each) in 5 ml of benzene is then injected from a side ampule into the reaction mix, and the pressure of hydrogen adjusted to 40–100 atm. The course of reduction to amine is monitored by withdrawing small (1–2 ml), clear, yellow liquid samples at regular time periods, and analyzing them by GLC. Once the pattern of sequential hydrogenation of a particular nitroaromatic substrate mixture has been established, hydrogenation may be arrested at the appropriate time by rapid cooling of the reactor, and by removal of the hydrogen. The product amines may be isolated by solvent extraction.

Results

General Synthesis. Various soluble ruthenium and iron complexes have been screened for nitroaromatic hydrogenation,[6] particularly those complexes known to catalyze homogeneous hydrogenation reactions,[2-4] and/or transformations of the $C-NO_2$ function.[4,10] Dichlorotris(triphenylphosphine)ruthenium(II) proved to be an excellent catalyst for the selective reduction of $PhNO_2$ to amine (see Table I) even at initial substrate/catalyst mole ratios of 200 or more. Ruthenium carbonyl complexes like $RuCl_2(CO)_2(PPh_3)_2$ show comparable activity; the dimeric $[Ru(CO)_3Cl_2]_2$ complex, lacking organophosphine ligands, undergoes some degradation to the metal (expt 3). Related complexes of iron(II), such as $FeCl_2(PPh_3)_2$, are unsuitable because of their extreme lability, particularly in hydroxylic solvents.[11] The more stable phosphine substituted iron(0) carbonyls, like $Fe(CO)_3(PPh_3)_2$, that are known to undergo a variety of oxidative-elimination reactions,[12] proved more promising (expt 6), and upon conclusion of the reduction, crystalline $Fe(CO)_3(PPh_3)_2$ may be recovered unchanged.

Table I. Nitrobenzene Hydrogenation in the Presence of Various Iron and Ruthenium Complexes[a]

Expt	Catalyst composition	Registry no.	Reaction time, min	Nitrobenzene conversion, %	Aniline selectivity, %
1	$RuCl_2(PPh_3)_3$	15529-49-4	420	>99	90
2	$RuCl_2(PPh_3)_3$[b]		200	99	89
3	$(RuCl_2(CO)_3)_2$[c]	25594-69-0	220	>99	85
4	$RuCl_2(CO)_2(PPh_3)_2$	14564-35-3	420	>99	96
5	$Ru(CH_3COCHCOCH_3)_3$[c]	14284-93-6	240	24	95
6	$Fe(CO)_3(PPh_3)_2$	14741-34-5	500	>99	87
7	$Fe(CO)_3(AsPh_3)_2$[c]	14375-85-0	180	>99	94
8	$Fe(CO)_5$[c]	13463-40-6	420	31	>95
9	Fe(naphthenate)$_3$	1338-41-3	240	7	>90

[a] Run conditions: 1.6 mM [Ru] or [Fe]; 0.32 M $PhNO_2$; 125°C; 80 atm H_2; benzene–ethanol (1:1) solvent. [b] 3.0 mM [Ru], 0.30 M $PhNO_2$; 135 °C. [c] Some catalyst decomposition during these runs as evidenced by the precipitation of insoluble ruthenium or iron species.

Table II. Nitrobenzene Hydrogenation Catalyzed by $RuCl_2(PPh_3)_3$ in Various Solvent Media

Expt	Solvent media	$[PhNO_2]/[Ru]$ ratio	Reaction: Temp, °C	Reaction: H_2 pressure, atm	Reaction: Time, min	Nitrobenzene conversion, %	Aniline selectivity, mol %
10	Benzene–ethanol–KOH[a]	200	130	89	45	>99	96
11	Benzene–ethanol–KOH[a]	50	25	82	570	>99	95
12	Benzene–ethanol–KOH	50	25	20	570	35	78
13	Benzene–ethanol–KOH	50	25	1	460	<5	76
14	Benzene–ethanol[b]	200	130	80	420	>99	89
15	Benzene	200	120	82	300	30	>99
16	Benzene–ethanol–acetic acid[c]	200	135	82	250	>99	92

[a] Run conditions: 3.6 mM $RuCl_2(PPh_3)_3$; 0.14 M KOH; benzene–ethanol (5:2 v/v). [b] 3.0 mM $RuCl_2(PPh_3)_3$; benzene–ethanol (1:1 v/v). [c] 5% (v/v) concentrated glacial acetic acid.

Although $Fe(CO)_3(PPh_3)_2$ is generally less effective than $RuCl_2(PPh_3)_3$ and related ruthenium complexes (cf. expt 1–6), it is considerably more active than iron pentacarbonyl in this application. Bis(triphenylphosphine)tricarbonyliron(0), on the other hand, which more readily undergoes initial dissociation,[3,12] and which shows greater specific activity (expt 7), is also subject to degradation during the $PhNO_2$ reduction, as evidenced by the formation of insoluble iron hydroxyl species. Analogous iron and ruthenium complexes have been found active for both the sequential hydrogenation of nitroaromatics (see below), and for the reduction of nitroaliphatics.[5]

Effect of Reaction Parameters. Dichlorotris(triphenylphosphine)ruthenium(II), the standard catalyst precursor in much of this work, is readily soluble in 1:1 benzene–ethanol,[13] and hydrogenation proceeds under these conditions to give aniline, and other aromatic amines, in at least 85 mol % selectivity (expt 14, Table II). The stoichiometry of eq 1 is confirmed by Karl Fischer titrations. *N*-Ethylaniline is a major by-product from nitrobenzene reduction, together with trace amounts of *N,N*-diethylaniline. Hydrogenation is generally more rapid in alkali-treated benzene–ethanol, and even at nitrobenzene/Ru molar ratios of 200, reduction may be completed within 1 h (expt 10). Furthermore, aniline is produced in near-quantitative yields. The enhanced activity of $RuCl_2(PPh_3)_3$ by base additives has been noted previously for the selective hydrogenation of certain 3-oxo-1,4-diene steroids.[14] In both cases, the improved activity may be attributed to the base-promoted formation of intermediate ruthenium–hydride complexes such as that depicted in eq 2.[15]

$$RuCl_2(PPh_3)_3 + H_2 + \text{base} \rightleftharpoons RuHCl(PPh_3)_3 + \text{base·HCl} \quad (2)$$

In the absence of alkali, the ethanol cosolvent, or the aromatic amine product, may serve as less effective promoters of the hydride formation step. This is consistent with considerably slower hydrogenation rates in benzene alone (expt 15), and similar rates for $RuCl_2(PPh_3)_3$ and $RuHCl(PPh_3)_3$ in benzene–ethanol.[5] The addition of organic acids, in the form of a 5% concentration of glacial acetic acid, does not significantly alter the aniline selectivity (cf. expt 14 and 16), and there is no evidence for p-aminophenol, such as might be generated if phenylhydroxylamine were involved in the reduction sequence.[16]

The development of accurate kinetic data for reaction 1 has been hampered by the poor reproducibility of the rate measurements, and induction periods at high $(PhNO_2)/(Ru)$ ratios. The poor reproducibility may be due to the extreme sensitivity of the catalyst solutions to dissolved oxygen,[13,17] the use of mixed solvent media, and the effect of the amine products, which are known to complex directly with ruthenium(II)–triphenylphosphine complexes,[18] and to shift the equilibria (2). Initial rate studies, designed to minimize the effects of the aniline product, were found to obey a first-order dependence upon ruthenium catalyst concentration over the range 1.0–5.0 mM [Ru] at moderate $[PhNO_2]/[Ru]$ ratios of ca. 100. The apparent faster rates at lower [Ru] are indicative of increased dissociation of the $RuHCl(PPh_3)_3$ complex[19] and/or the possible importance of more than one catalytically active species.[20,21] It has been estimated[22] that at 25 °C, K (eq 3) $< 10^{-5}$, but more extensive dissociation is likely at 100–130 °C owing to thermal stimulation.

$$RuHCl(PPh_3)_3 \rightleftharpoons RuHCl(PPh_3)_2 + PPh_3 \quad (3)$$

Consistent also with this displacement of ligand from $RuHCl(PPh_3)_3$, we find a small inverse dependence of the rate upon added PPh_3. In comparative experiments, the addition of a two molar excess of PPh_3 ([Ru] = 2 mM) resulted in a 45% drop in reaction rate, and slower rates with further quantities of PPh_3.

Figure 1[38] shows how the measured rate varies linearly with applied H_2 pressure. Rates of deuteration are slower, with a kinetic isotope ratio (k_H/k_D) of 1.47; this is in spite of competing D_2–ethanol exchange. Amine formation is extremely slow under ambient conditions (Table II, expt 13) and in contrast to the rapid hydrogenation of 1-alkenes

Table III. Hydrogenation of Substituted Nitroaromatics[a]

Expt	Nitroaromatic	Registry no.	Nitroaromatic conversion, %	Major products: Identity	Major products: Selectivity, mol %
17	*p*-Nitrotoluene	99-99-0	84	*p*-Toluidine	92
18	4-Nitro-*o*-xylene	99-51-4	79	3,4-Xylidine	81
19	2-Nitro-*m*-xylene	81-20-9	63	2,6-Xylidine	92
20	1-Nitronaphthalene	86-57-7	65	1-Aminonaphthalene	91
21	1-Chloro-4-nitrobenzene	100-00-5	99	4-Chloroaniline	89
22	1-Bromo-4-nitrobenzene	586-78-7	99	4-Bromoaniline	67
23	4-Nitrophenol	100-02-7	99	*p*-Aminophenol	96
24	4-Nitroanisole	100-17-4	91	*p*-Anisidine	81
25	*p*-Nitrobenzonitrile	619-72-7	77	*p*-Aminobenzonitrile	78
26	2-Nitrothiophene	609-40-5	<1		
27	5-Nitroquinoline	607-34-1	99	5-Aminoquinoline	51
28	*ω*-Nitrostyrene	103-64-0	17[b]	2-Phenylnitroethane	>80
29	Ethyl *p*-nitrocinnamate	953-26-4	42[c]	Ethyl *p*-nitro-2-phenylpropionate Ethyl *p*-amino-2-phenylpropionate	83 14

[a] Standard run conditions: 2.5 mM $RuCl_2(PPh_3)_3$; 0.25 M $PhNO_2$; 135 °C; 80 atm H_2; 300 min. [b] Run at 25 °C for 24 h. [c] Run at 105 °C for 120 min.

under subatmospheric pressures of hydrogen,[13] only upon going to superatmospheric H_2 pressures is it possible to generate aniline at reasonable rates (expt 11).

Hydrogenation of Substituted Nitroaromatics. Selective C–NO_2 hydrogenation by $RuCl_2(PPh_3)_3$ has been demonstrated in the presence of a variety of substituent groups, including chloride, bromide, hydroxide, alkoxide, alkyl, aryl, and ester groupings (see Table III). No reduction was detected with S heterocyclics such as 2-nitrothiophene (expt 26), but 5-aminoquinoline was obtained in 51% yield from 5-nitroquinoline. This constrasts with the reported deactivation of *RuHCl*$(PPh_3)_3$ by pyridine and its derivatives in the case of alkene hydrogenation[13] and the formation of isolable complexes with heterocycles like 2,2′-bipyridyl.[13,23]

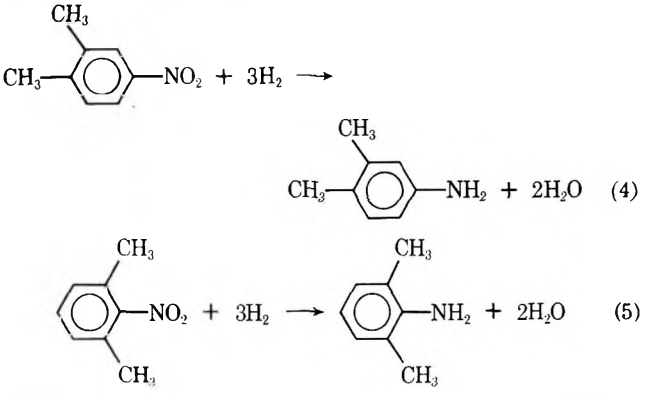
Since $RuCl_2(PPh_3)_3$ is well recognized as a catalyst precursor for selective alkene hydrogenation,[13,19] it was of interest to examine the performance of the complex with certain nitro olefins. Two nitro olefins were considered under standard hydrogenation conditions (see Table III). Reduction of ethyl *p*-nitrocinnamate takes place in two distinct steps. The initial reaction is reduction of the unsaturated carbon–carbon double bond to give ethyl *p*-nitro-2-phenylpropionate, and only after some 35% of the *p*-nitrocinnamate ester has reacted is a second reduction step, of the *p*-nitro group to amine, in evidence. The final product is ethyl *p*-amino-2-phenylpropionate.

ω-Nitrostyrene is subject to rapid polymerization under similar conditions, and in the presence of alkali, but at ambient temperatures, selective reduction to 2-phenylnitroethane has been observed (expt 28); small quantities of fully reduced phenethylamine were also detected. Nitronitriles such as *p*-nitrobenzonitrile lead to moderate yields of the corresponding aminonitrile, with only minor amounts of diamine.

For certain of the para-substituted nitroaromatics listed in Table III, the initial rates of hydrogenation have been measured under standard conditions, and a linear plot of the logarithm of their relative rates vs. Hammett's substituent constants is shown in Figure 2.[38]

Generally an increase in the electron-withdrawing capability of the para substituent (i.e., H → NO_2) is paralleled by an increase in hydrogenation rate. Conversely, electron-donating substituents, which tend to increase the electron density on the nitro function, and thereby lower the polarization of the N–O bonds,[24,25] lead to slower rates of hydrogenation.

Sequential Reduction of Nitroaromatic Mixtures. In order to fully explore possible areas of novelty for the $RuCl_2(PPh_3)_3$ catalyst, the course of C–NO_2 reduction has been followed in a series of competitive experiments with mixtures of variously substituted nitroaromatics. In the first experimental series, equimolar mixtures of certain alkylated nitrobenzenes were subjected to $RuCl_2(PPh_3)_3$ catalyzed hydrogenation to determine if the ruthenium catalyst would preferentially act upon particular classes of structure. Two sets of experiments exemplifying a sequential hydrogenation technique are illustrated in Figures 3 and 4. Figure 3 shows the case for an equimolar charge of two nitroxylene isomers, 4-nitro-*o*-xylene and 2-nitro-*m*-xylene; the initial reaction is preferential reduction of the 4-nitro-*o*-xylene isomer to 3,4-xylidine (eq 4), and only after some 90% of this material has been reduced to amine is any significant quantity of the 2-nitro-*m*-xylene converted to 2,6-xylidine (eq 5).



The ruthenium catalyst proved to be equally selective in the case of equimolar mixtures of nitromesitylene and nitrobenzene (Figure 4).[38] Here, at least 95% of the nitrobenzene is hydrogenated to aniline prior to reduction of the nitromesitylene to mesidine.

The two cited examples of sequential hydrogenation do, of course, represent particular circumstances where one nitroaromatic component has both ring positions ortho to the nitro group filled by alkyl groups, whereas the second component has no ortho substituents. Even so, with other two-component mixtures where, for example, one component has two ortho substituents and the other has only one (e.g., mixtures of 4-nitro-*m*-xylene and 2-nitro-*m*-xylene), then sequential hydrogenation is still possible with the $RuCl_2(PPh_3)_3$ catalyst (see Table IV). Generally, to ensure sequential hydrogenation of alkylated nitrobenzene mixtures with this class of catalyst, it is necessary only that at

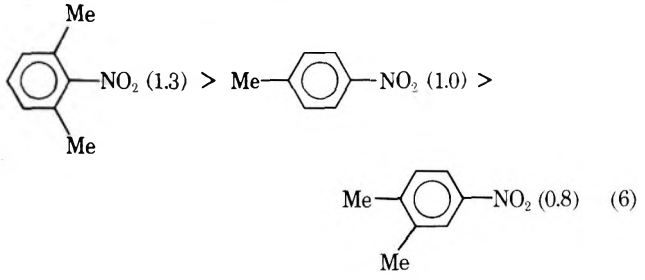
Table IV. Sequential Hydrogenation of an Equimolar Nitroxylene Mixture[a]

Time from start of hydrogenation, min	Conversion of 4-Nitro-*m*-xylene to 2,4-xylidine, mol %	Conversion of 2-Nitro-*m*-xylene to 2,6-xylidine, mol %
15	13	<1
30	27	<1
45	39	2
60	50	4
90	75	11
120	>99	22
180	>99	50
240	>99	76
300	>99	98

[a] Run conditions: 4.0 mM $RuCl_2(PPh_3)_3$; 0.20 M; $C_8H_9NO_2$; 125 °C; 80 atm H_2.

least one component be disubstituted ortho to the NO_2 function. It is only where there is no diortho substitution, as in the case of mixtures of 4-nitro-*o*-xylene and 4-nitro-*m*-xylene, that the $RuCl_2(PPh_3)_3$ fails to discriminate.

The unique selectivity exemplified here for $RuCl_2(PPh_3)_3$-catalyzed nitroaromatics hydrogenation is in some ways akin to the selective hydrogenation of alkene–alkyne mixtures.[26] In both applications, the observed sequential hydrogenation is likely the result of preferential complexation with the ruthenium catalyst ($K_{\text{substrate 1}} > K_{\text{substrate 2}}$) rather than due to the kinetic effect of marked differences in the hydrogenation rates ($k_{\text{substrate 1}} < k_{\text{substrate 2}}$).[19] Certainly in the case of alkylated nitrobenzenes, both hindered and nonhindered, we find the individual rates of hydrogenation to vary by less than a factor of 2 in the order of eq 6 (relative rates in parentheses).



(6)

On the other hand, in competitive experiments with mixtures of substituted nitrobenzenes, as described above, there is little or no reduction of the ortho-substituted components during the course of reduction of the less sterically crowded derivatives.

Sequential Hydrogenation of Nitroaromatic–Nitrobinuclear Aromatic Mixtures. Competitive experiments designed to determine the effect of a second phenyl ring adjacent to the nitro function[27,28] have served to demonstrate that (a) with an equimolar 1-nitronaphthalene–nitrobenzene mixture, the $RuCl_2(PPh_3)_3$ solutions are selective for 1-nitronaphthalene hydrogenation only up to about 30% conversion, beyond 30% both substrates are reduced concurrently, and (b) with an equimolar mixture of 1-nitronaphthalene and the sterically hindered 2-nitromesitylene, reduction of the nitronaphthalene to α-napthylamine is essentially complete (>95% conversion) before nitromesitylene reduction to mesidine gets under way. Other ruthenium complexes, including $RuCl_2(CO)_2(PPh_3)_2$ and $RuCl_2(SbPh_3)_3$, display similar selectivity patterns, but analogous iron complexes proved nonselective under these conditions.

Selective Hydrogenation of Dinitroaromatics. The performance of the $RuCl_2(PPh_3)_3$ catalyst is illustrated here for several typical dinitroaromatics, including *m*-dinitrobenzene and *p*-nitrobenzene. The increase in initial rate of nitroaromatic hydrogenation caused by introducing a second para NO_2 substituent has already been noted in Figure 2. The results of a typical run with *p*-dinitrobenzene are reproduced in Figure 5. The initial reaction is selective reduction of the *p*-dinitrobenzene to *p*-nitroaniline (eq 7), and only after 85–90% of the starting dinitro compound has been reduced to the intermediate *p*-nitroaniline is *p*-phenylenediamine (eq 8) detected in the reaction mix.

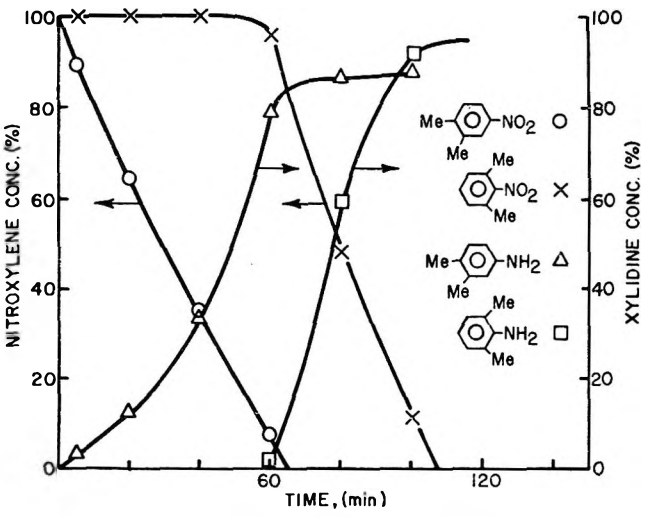


Figure 3. The sequential hydrogenation of equimolar nitroxylene mixture: (a) ○, 4-nitro-*o*-xylene; ×, 2-nitro-*m*-xylene; △, 3,4-xylidine; □, 2,6-xylidine. (b) Run conditions: 5.0 mM $RuCl_2(PPh_3)_3$; 0.26 mM $C_8H_9NO_2$; 135 °C; 80 atm H_2.

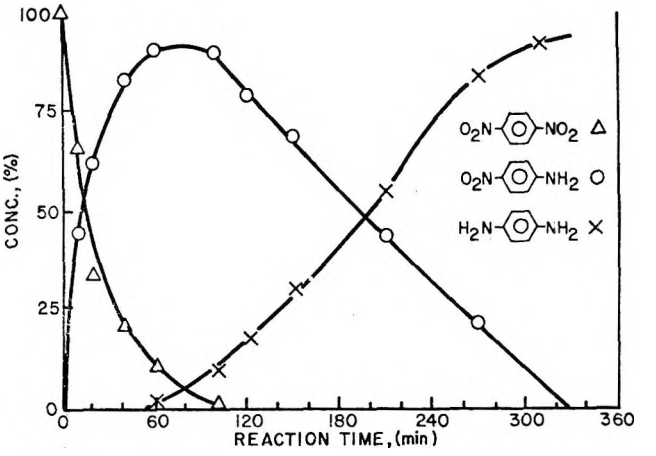
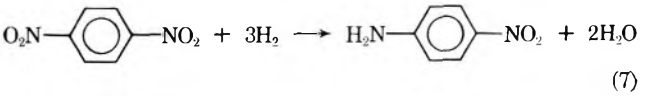
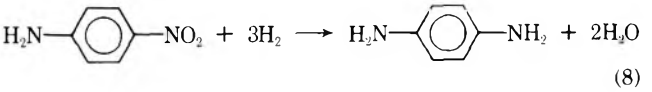


Figure 5. The selective hydrogenation of *p*-dinitrobenzene: (a) △, *p*-dinitrobenzene; ○, *p*-nitroaniline; ×, *p*-phenylenediamine. (b) Run conditions: 2.5 mM $RuCl_2(PPh_3)_3$; 0.25 M $C_6H_4(NO_2)_2$, 135 °C; 80 atm H_2.



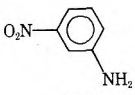
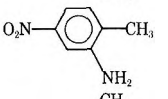
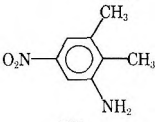
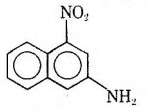
(7)



(8)

This high selectivity for the intermediate nitro amine is unusual in the catalytic hydrogenation of nonhindered polynitro compounds.[29] Smith, for example, reports[30] the hydrogenation of polynitroaromatics over Adams' platinum catalyst to proceed without breaks in the kinetic curves. In these experiments (Figure 5), after initial hydrogenation of the *p*-dinitrobenzene, there is expected to be a competition between the *p*-dinitrobenzene and the newly formed *p*-nitroaniline for the available coordination sites on the ho-

Table V. Selective Hydrogenation of Dinitroaromatics[a]

Dinitroaromatic	Registry no.	Reaction time, min	Dinitroaromatic conversion, %	Major product: Identity[b]	Major product: Selectivity, mol %
m-Dinitrobenzene	99-65-0	210	77		73
2,4-Dinitrotoluene	121-14-2	180	42		91
3,5-Dinitro-*o*-xylene	616-69-3	180	59		68
1,3-Dinitronaphthalene	606-37-1	120	95		71

[a] Run conditions: 4.0 mM $[RuCl_2(PPh_3)_3]$; 0.1–0.2 M $[Ph(NO_2)_2]$; 125 °C; 80 atm H_2. [b] Identification by NMR, ir, GLC, and, in some cases, by elemental analyses.

mogenous ruthenium catalyst. The difference then in electron density on the coordinating C–NO_2 groups, due to electron withdrawal by the second *p*-NO_2 of the *p*-dinitrobenzene (σ +0.78) vs. *p*-NH_2 electron donation (σ −0.66),[31] appears to play an important role in ensuring preferential bonding with the dinitro component. The result is the high yield of the partially reduced *p*-nitroaniline.

The relative difference in the resonance effects of the NO_2 and NH_2 group will, of course, be diminished in the case of *m*-dinitrobenzene. Here, under the conditions of Figure 5, the concentration of *m*-nitroaniline reaches only 56% of theoretical, and *m*-phenylenediamine is detected after only 60% of the *m*-dinitrobenzene has been converted. Apparently, the inductive and/or steric influences of the meta NO_2 and NH_2 substituents are insufficiently different to ensure high selectivity for the *m*-nitroaniline intermediate. A combination of both steric and electronic effects are in evidence for dinitrotoluenes, dinitroxylenes, and dinitronaphthalenes (see Table V).

Sequential Hydrogenation of Dinitroaromatic–Nitroaromatic Mixtures. The ability of the homogeneous $RuCl_2(PPh_3)_3$ catalyst to selectively hydrogenate dinitroaromatics to their partially reduced species may be put to advantage where one wishes to sequentially hydrogenate dinitroaromatics in the presence of mononitro materials.[32]

In a typical experiment, an equimolar mixture of *p*-dinitrobenzene (13 mmol) and nitrobenzene (13 mmol) was hydrogenated in benzene–ethanol solution containing 0.25 mmol of $RuCl_2(PPh_3)_3$ under normal operating conditions, and reduction followed by GLC as a function of time. The following reaction sequence was observed (see data in Figure 6).

(1) Initial selective reduction of *p*-dinitrobenzene to *p*-nitroaniline.
(2) Hydrogenation of the nitrobenzene component to aniline.
(3) Hydrogenation of the *p*-nitroaniline intermediate to *p*-phenylenediamine.

It is considered particularly significant that almost all (>90%) of the *p*-dinitrobenzene component is converted to *p*-nitroaniline prior to any significant reduction of the nitrobenzene, but that once the second stage is underway (10–15% $C_6H_5NO_2$ conversion to aniline) reduction of the nitrobenzene and the *p*-nitroaniline intermediate take place concurrently.

From similar studies it is concluded that the technique is applicable to a variety of polynitroaromatic–mononitroaromatic mixtures. Both para and meta dinitroaromatics may be selectively reduced to the substantial exclusion of mononitroaromatic components using other ruthenium complexes,[7] including $RuCl_2(CO)_2(PPh_3)_2$, $RuCl_2(SbPh_3)_3$, and $RuCl_3(PPh_3)_2$. Data for a typical *m*-dinitrobenzene–nitrobenzene mix are summarized in Figure 7.[38] The reaction sequence is as follows.

(1) Initial selective reduction of the *m*-dinitrobenzene to *m*-nitroaniline.
(2) Concurrent hydrogenation of the *m*-nitroaniline and nitrobenzene components to their respective amines.

Again, it is considered significant that reduction of the *m*-dinitrobenzene component is essentially complete (>95% conversion) before there is any detectable reduction either of the nitrobenzene component or the *m*-nitroaniline intermediate.

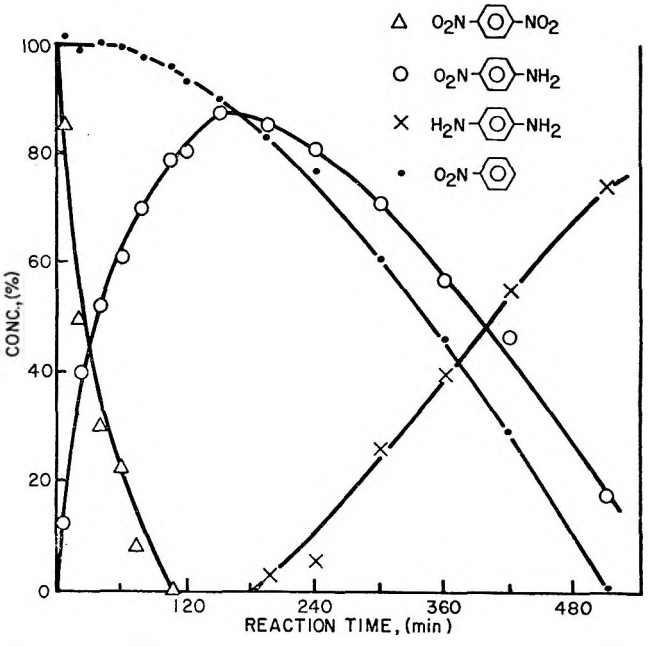


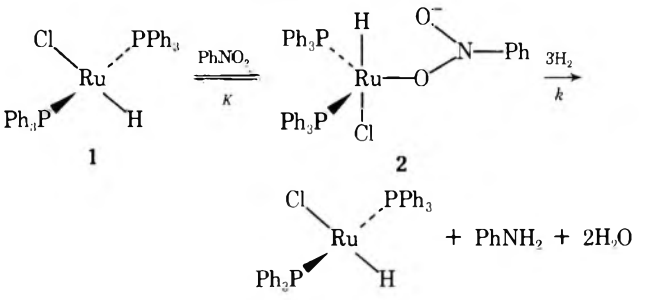
Figure 6. The sequential hydrogenation of an equimolar *p*-dinitrobenzene–nitrobenzene mixture: (a) Δ, *p*-dinitrobenzene; O, *p*-nitroaniline; ×, *p*-phenylenediamine; nitrobenzene. (b) Run conditions: 2.5 mM $RuCl_2(PPh_3)_3$; 0.13 M $C_6H_4(NO_2)_2$; 0.13 M $C_6H_5NO_2$, 135 °C; 80 atm H_2.

Discussion

The data described above feature the following. (a) The application of homogeneous catalysis to the selective hydrogenation of the C–NO_2 function in a variety of nitroaryls. (b) Techniques for sequentially hydrogenating polynitroaromatics and polynitro–mononitroaromatic mixtures where the ruthenium catalyst appears particularly sensitive to the degree of N–O bond polarization. (c) A method of sequentially hydrogenating certain alkylated nitroaromatic mixtures which may be ascribed to catalyst sensitivity to steric factors, particularly the "ortho" effect.[30]

Extensive studies of hydrogen activation by solutions of the $RuCl_2(PPh_3)_3$ complex[13-15,33-35] have generally been interpreted[36] in terms of initial ruthenium–hydride formation (eq 2) followed by at least partial dissociation to the *trans*-$RuHCl(PPh_3)_2$ complex (1) in accordance with eq 3. Our data (vide supra), particularly the sensitivity of $PhNO_2$ hydrogenation to added base, inhibition by excess ligand, and similar rates for $RuCl_2(PPh_3)_3$ and $RuHCl(PPh_3)_3$ solutions,[5] are in accord with the intermediate formation of 1. Furthermore, the spectra of recovered catalyst samples show ν(Ru–H) at ca. 2020 cm^{-1}. Subsequent interaction of 1 with nitroaryl to yield amine products (Scheme I) likely proceeds via proton transfer and repeated oxidative addition of molecular hydrogen to give octahedral ruthenium(IV)–hydrido species,[19] reductive elimination of amine and the elements of water completing the catalyst cycle. Discrete nitrene species are unlikely to be important in view of the lack of evidence for coupling products,[4b] particularly azo- and hydrazobenzenes, but coordinated nitroso species cannot be discounted since we find the rate of nitrosobenzene reduction to be faster than for nitrobenzene. The sensitivity of the $PhNO_2$ reduction to hydrogen pressure and [Ru] and the small kinetic isotope effect are consistent with oxidative H_2 addition being rate limiting. The fact that no amine is detected in the benzene–ethanol media in the absence of H_2 (see also ref 5) makes it unlikely that ethanol cosolvent is an important alternative hydride source here. This is in spite of recent reports of $RuCl_2(PPh_3)_3$-catalyzed hydrogen transfer.[37] Likewise, $RuHCl(PPh_3)_3$ ortho metalation, which has recently been applied to the stoichiometric reduction of alkenes,[22] is normally slow compared to hydrogenation.[13,22]

Scheme I. Nitroaryl Hydrogenation Catalyzed by $RuHCl(PPh_3)_2$



In spite of the complexities of this catalysis, the unique selectivity data exemplified in Figures 3–7 may be rationalized largely on the basis of competitive substrate interaction with the ruthenium metal center at some stage during the hydrogenation sequence. Similar hydrogenation rates for individual hindered and nonhindered nitroalkylbenzenes (eq 6) point to the relative insensitivity of the slow steps of this catalysis to the bulk of the coordinated nitroaryl molecule, or its partially reduced derivatives. On the other hand, the high selectivity evident during sequential hydrogenation of nitroalkylbenzene mixtures (Figures 3 and 4) suggests widely different complexity constants for the nitroaromatics and ortho-alkylated nitroaromatics bonded to ruthenium in 2 or some latter intermediate, and preferential complexation with the least hindered isomer (e.g., $K_{nitroaromatic} > K_{nitroalkylaromatic}$). At least two factors may play a critical role. Firstly, the sterically crowded five coordinate complex 2 accommodates two bulky triarylphosphine ligands, and will therefore bond preferentially with the least sterically hindered nitroaryl substrate available. Secondly, in the case of diortho substituted nitroaryls, such as 2-nitromesitylene and 2-nitro-*m*-xylene, the ortho methyl groups force the nitro group out of the plane of the aromatic ring,[30] thereby preventing free resonance between the aryl and NO_2 functions, and further increasing the effective size of the $PhNO_2$ molecule perpendicular to the plane of the ring.

Steric factors appear to have less influence in the case of sequential polynitroaromatic hydrogenation. The moderate differences in rates for para-substituted nitrobenzenes (Figure 2) point to the degree of polarization of the N–O bonds as significantly affecting the electron density at the metal center in intermediates such as 2, and therefore the ease of rate-determining hydrogenation (i.e., $k_{dinitroaromatic} > k_{mononitroaromatic}$). It is unlikely, however, that these differences in rate could, by themselves, account for the observed sequential hydrogenation of dinitroaromatics and dinitro–mononitroaryl mixtures. A second, reinforcing factor would be preferential complexation of the more polar dinitroaromatic components with the catalytically active ruthenium–hydrido species (e.g., 2, $K_{dinitroaromatic} > K_{mononitroaromatic}$). Certainly this would be consistent with the improved selectivity observed in hydrogenating para vs. meta dinitrobenzenes (Figure 5, Table V), and with the order of sequential hydrogenation exemplified in Figures 6 and 7.

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Registry No.—2,6-Xylidene, 87-62-7; 4-nitro-*m*-xylene, 89-87-2.

Supplementary Material Available. Figures 1, 2, 4, and 7 (4 pages). Ordering information is given on any current masthead page.

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Palladium-Catalyzed Vinyl Substitution Reactions. II. Synthesis of Aryl Substituted Allylic Alcohols, Aldehydes, and Ketones from Aryl Halides and Unsaturated Alcohols

Alan J. Chalk* and Steven A. Magennis

Givaudan Corporation, Clifton, New Jersey 07014

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A variety of substituted bromo- and iodobenzenes reacted with 2-methyl, 1-methyl, and 1-1-dimethyl allyl alcohols to give aryl substituted aldehydes, ketones, and allyl alcohols, respectively. Bromo- and iodobenzene reacted in a similar manner with some nonallylic unsaturated alcohols. In these cases, the double bond migrated along the carbon chain until captured by the alcohol function to give a carbonyl product. Formation of the intermediate phenyl substituted unsaturated alcohols was minimal unless a quaternary carbon separated the double bond and alcohol functions.

Phenyl substituted carbonyl compounds can be prepared by the palladium-catalyzed reaction of iodobenzene and bromobenzene with allylic alcohols.[1] Heck and co-worker have described a related reaction in which considerable amounts of phenyl substituted unsaturated alcohols were also formed, particularly from the bromo compounds.[2] The reaction was shown to apply to homoallylic alcohols, but again a mixture of products was formed.

In the present paper our work is extended to the reaction of a variety of substituted aryl halides with allylic alcohols and to the reaction of bromobenzene and iodobenzene with some nonallylic unsaturated alcohols. Since the major products were carbonyl compounds even when aryl bromides were used, the reaction has considerable synthetic utility.

Results

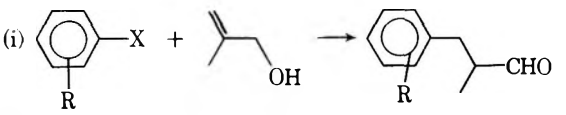
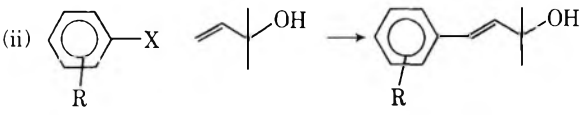
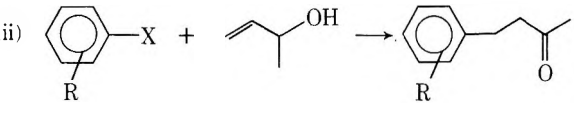
Reaction of Substituted Aryl Halides with Allylic Alcohols. The reactions summarized in Table I, parts i and iii, gave predominantly carbonyl compounds as products. Variations in the catalyst and solvent have no special significance, but special conditions were used in some cases to achieve better yields. Where a GC yield is quoted, the product was also isolated and identified in earlier experiments.

Although a wide variety of substituents were tolerated, there were side reactions which appeared to relate to the electron-donating character of the substituent. Thus, the reaction of the 4-nitroiodobenzene gave a 20% yield (isolated) of 4,4′-dinitrobiphenyl which is a fourfold increase over the amount of biphenyl produced from iodobenzene under corresponding conditions.

With electron-donating substituents (OH, OMe, OCH_2O) another side reaction developed, namely reduction of the aryl halide. This occurred in reactions with 1-buten-3-ol, and to a lesser extent with 2-methyl-2-propen-1-ol. This reduction was more significant with the bromide than the iodide and was more pronounced when a tertiary amine was used as base in place of sodium bicarbonate. Thus, in the reaction of 4-iodophenol and 1-buten-3-ol the yields of 4-(4′-hydroxyphenyl)-2-butanone and phenol were 36 and 44%, respectively, when triethylamine was used as base. However, when sodium bicarbonate was used as base with only a catalytic amount of triethylamine, these yields changed to 77 and 2%. In the reaction of 3,4-methylenedioxybromobenzene with methallyl alcohol, methylenedioxybenzene was the sole product when tripropylamine was used as base. However, the use of sodium bicarbonate with or without a catalytic amount of tripropylamine gave yields of approximately 50% of the expected aldehyde.

A further complication was found with 4-alkylbromobenzenes. Although the corresponding iodides reacted satisfactorily, the bromides reacted slowly and palladium metal formed early in the reaction, which stopped at only a partial conversion. A variety of different solvents, bases, and phosphines were tried with 4-*tert*-butylbromobenzene but the best yields were obtained when sodium iodide was used in place of triphenylphosphine. Sodium iodide was used in the hope that halogen exchange might occur to give the 4-*tert*-butyliodobenzene. No evidence for this exchange was found, but the desired product was formed under mild conditions (110 °C) in the absence of phosphine. The reaction rate, conversion, and yield all increased with an increasing amount of the solvent (hexamethylphosphoramide, HMP).

Table I. Reactions of Aryl Halides with Allylic Alcohols[a]

R	X	Temp, °C	Time, h	Conversion,[b] %	Yield,[c] %
(i) 					(1)
2-CH_3	I	140	0.7	100	77
4-OCH_3	I	125	16.5	100	61
4-OH	I	130	2.5	100	42
4-NO_2	I	130	5.5	100	50
4-*t*-Bu	I	130	6	100	95[d]
4-COOEt[e,f]	Br	130	0.7	100	82
4-CHO	Br	130	7	100	57
4-CN	Br	130	4	79	52
4-CH_3CO[f]	Br	130	2	100	35
3,4-OCH_2O[g,h]	Br	135	4	80	52[d]
4-*t*-Bu[f,i]	Br	110	4	86	82
4-*i*-Pr[f,i]	Br	110	10	93	72
(ii) 					(2)
4-OCH_3[e,f,j]	Br	130	3.5	100	59
4-CH_3CO[f,k]	Br	110	2.5	100	67
4-CH_3[f,h,l]	Br	120	3	100	80
(iii) 					(3)
4-OH[f,m]	I	120	3.5	87	77[d]
4-CH_3CO[f]	Br	130	2	100	35

[a] 50 mmol of aryl halide, 75 mmol of allylic alcohol, 60 mmol of $NaHCO_3$, 0.45 mmol of $PdCl_2$ with 0.9 mmol of PPh_3 if X = Br, 20 ml of *N*-methylpyrrolidinone (unless otherwise specified). [b] Conversion of aryl halide by GC. [c] Isolated yield based on 100% conversion except as noted. [d] Yield by GC (internal standard). [e] Hexamethylphosphoramide used as solvent. [f] $PdOAc_2$ used in place of $PdCl_2$. [g] 1 mmol of tripropylamine added. [h] Dimethylformamide as solvent. [i] 60 ml of hexamethylphosphoramide as solvent and PPh_3 replaced by 16.5 mmol of NaI. [j] 8 mmol of diisopropylethylamine added. [k] 2.5 mmol of trilaurylamine added. [l] 2.3 mmol of trioctylamine added. [m] 1 mmol of triethylamine added, dimethylacetamide as solvent.

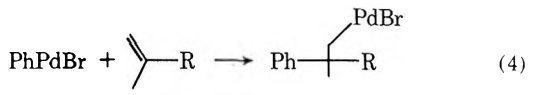
Thus, when the volume of solvent was increased from the usual 20 ml to 40 ml and then to 60 ml, the conversion and yield increased dramatically (conversions, 19, 76, and 86%; yields 14, 60, and 76%, respectively).

An interesting by-product, 3-phenyl-2-methylpropanal, was formed in the reaction of 4-*tert*-butylbromobenzene and methallyl alcohol. The amount of this side product was proportional to the amount of triphenylphosphine used in the reaction and was completely absent when triphenylphosphine was omitted. It therefore appears that a phenylpalladium intermediate was formed via the scission of a P–C_6H_5 bond. A similar reaction has been reported between triphenylphosphine and styrene to give stilbene.[3] The reaction was confirmed by the formation of 3-(methoxyphenyl)-2-methylpropanal when triphenylphosphine was replaced by tris(4-methoxyphenyl)phosphine.

The reaction between substituted aryl halides and 3-methyl-1-buten-3-ol gave good yields of the expected products providing the precautions used in preparing the unsubstituted analogue were followed.[1]

Nonallylic Alcohols. Table II shows that iodobenzene and bromobenzene may be treated with a variety of unsaturated alcohols to produce the corresponding phenyl substituted carbonyl compounds. Surprisingly, bromobenzene reacted faster than iodobenzene and it was noticed that palladium metal was formed more easily in the latter case. Similar small amounts of phenyl substituted unsaturated alcohols were formed in both cases.

For those alcohols having an isopropenyl group, one carbonyl product predominated. This was expected since the alternative mode of addition of phenylpalladium halide to the double bond (reaction 4) yields an intermediate which cannot eliminate palladium hydride to form an olefin. In the case of methallyl alcohol, however, reaction 4 does lead


(4)

to 5% of a product (2-methyl-2-phenylpropanal) which must be explained by a special mechanism.[1,2] Similar products were found in about 1% yield for three of the four alcohols which had an isopropenyl group listed in Table II. In each case a small GC peak occurring immediately before the main product (on both SE-30 and 20M columns) was identified by mass spectrometry. The molecular ion was

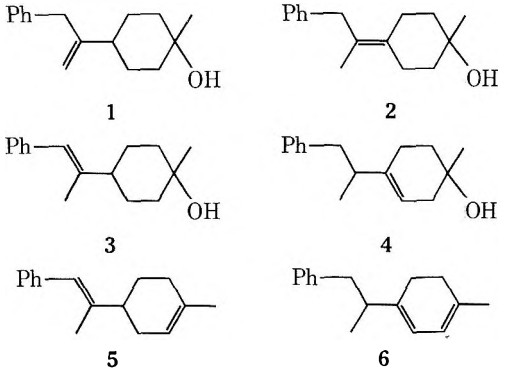
Table II. Reactions of Unsaturated Alcohols with Bromo- and Iodobenzene[a]

Alcohol	Halogen	Temp, °C	Time, h	Conversion, %	Product yields,[b] % Linear carbonyl	Branched carbonyl	Biphenyl	Unsaturated alcohols[c]
3-Buten-1-ol	I	130	2	100	44[d]	13[d]	4	3, 5
4-Penten-1-ol	I	130	2	98	30[d]	12[d]	Trace	Traces
3-Methyl-3-buten-1-ol	I	130	4	100	39[e]	~1	10	3, 4
3-Methyl-3-buten-1-ol	Br	130	3	100	58	~1	4	4, 5
5-Methyl-5-hexen-2-ol	I	130	22.5	100	40	~1	15	Trace, 9,[f] 16[g]
5-Methyl-5-hexen-2-ol	Br	120	7.5	100	49	~1	7	3, 9,[f] 11[g]
4-Methyl-4-penten-2-ol	I	130	24	86	48	~1	14	3,[h] 3,[i] 9[j]
4-Methyl-4-penten-2-ol	Br	120	17	100	56	~1	Trace	3,[h] 8,[i] 16[j]
4-Methyl-4-penten-1-ol	I	120	13	100	16		13	2, 4,[k] 2,[l] 4[m]
4-Methyl-4-penten-1-ol	Br	100	14	100	27		0	0, 4,[k] 6,[l] 8[m]

[a] 50 mmol of halobenzene, 75 mmol of alcohol, 60 mmol of $NaHCO_3$, 0.45 mmol of $PdCl_2$ or $PdOAc_2$, and in the case of C_6H_5Br, 2 mol of PPh_3 per mole of palladium in 20 ml of *N*-methylpyrrolidinone. [b] From GC using internal standards unless otherwise specified (based on 100% conversion). [c] Approximate yields based on GC using internal standard. Identification below by NMR. [d] Isolated yields. [e] In a second example, a 70% conversion (45% isolated yield) was obtained after 7 h at 110 °C. [f] Mixture of (*E*)- or (*Z*)-5-methyl-6-phenyl-5-hexen-2-ol, 5-methyl-6-phenyl-4-hexen-2-ol, and 5-benzyl-5-hexen-2-ol (~1:3:1). [g] (*Z*)- or (*E*)-5-methyl-6-phenyl-5-hexen-2-ol. [h] 4-Benzyl-4-penten-2-ol. [i] Mixture of 4-methyl-5-phenyl-4-penten-2-ol and 4-methyl-5-phenyl-3-penten-2-ol (~7:3). [j] (*E*)- or (*Z*)-4-methyl-5-phenyl-4-penten-2-ol. [k] 4-Benzyl-4-penten-1-ol. [l] (*E*)- or (*Z*)-5-phenyl-4-methyl-4-penten-1-ol. [m] (*Z*)- or (*E*)-5-phenyl-4-methyl-4-penten-1-ol.

found together with a large *m/e* 119 peak corresponding to the dimethylbenzyl group. In one case (3-methyl-3-phenyl-1-butanal), the mass spectral pattern fitted that obtained from an authentic sample, while in another case, sufficient material was isolated to identify it by NMR as the expected 4-methyl-4-phenyl-2-pentanone.

When a quaternary carbon atom separated the double bond and the alcohol function, phenyl substitution occurred to give unsaturated alcohols. Thus, 1-methyl-3-cyclohexene-1-methanol reacted with iodobenzene (18 h, 130 °C, in HMP) to give a 12% yield of phenyl substituted products. Eighty percent of the mixture was identified as 1-methyl-5-phenyl-3-cyclohexene-1-methanol and 20% as the isomer having either a 3- or 4-phenyl. Similarly β-terpineol (30 h, 130 °C in HMP) gave a 23% yield of a mixture of 9-phenyl substituted menthen-1-ols (8% **1**, 11% **2**, 27% **3**, and 54% **4**). In these cases, sodium bicarbonate was used as base with a catalytic amount of diisopropylethylamine. When the amine was used in stoichiometric amount in place of sodium bicarbonate, the products from β-terpineol suffered dehydration. Thus after 6.5 h at 130 °C, a 19% yield of phenyl substituted diolefins was obtained whose NMR spectrum was consistent with a mixture in which **5** and **6** predominated.



Biphenyl (29%) was also formed in this reaction which was not atypical.

For NMR data see paragraph at end of paper regarding supplementary material.

Discussion

The reaction of aryl halides with allylic alcohols was shown to be applicable to a wide variety of substituted iodides and bromides. Owing to competing side reactions, aryl bromides gave better results than iodides when the substituents were electron withdrawing while iodides gave the better results when the substituents were electron donating.

In the former case, the competing side reaction was biaryl formation which must result from the decomposition of the arylpalladium halide formed in reaction 5.[4]

$$ArX + Pd^0 \rightleftharpoons ArPdX \quad (5)$$

Reaction 5 is expected to be an equilibrium which is displaced to the right by electron-withdrawing substituents or by replacing X = Br by X = I. It is therefore also significant that in general biphenyl is a more important by-product of reaction 1 (R = H) when X = I than when X = Br.[1]

When the aryl substituent was electron donating, a competing side reaction caused reduction of the aryl halide. The principal hydrogen source was the alcohol since 1-buten-3-one was obtained from 1-buten-3-ol. Dimethylformamide may also be a hydrogen source since it appeared to promote the reduction more than other solvents. The reduction was most actively promoted by the amine hydrohalide which suggests reaction 6.

$$H^+ + ArPdX \longrightarrow ArH + PdX^+ \quad (6)$$

Reduction of PdX^+ to Pd^0 by the alcohol, followed by reaction 5, would complete the catalytic cycle for reduction.

The reaction mechanism previously discussed[1] suggests that the synthesis should be generally applicable to unsaturated alcohols. Providing the intermediate phenyl substituted olefins are not displaced from the coordination sphere of palladium, the double bond should shift along any carbon chain until "captured" by a hydroxyl function with the formation of a carbonyl group. This occurred under the experimental conditions used with certain unsaturated alcohols having as many as four carbon atoms separating the hydroxyl function from the double bond. Some unsaturated alcohols were formed, and the distribution of isomers was different for bromobenzene and iodobenzene. However, the total yield of unsaturated alcohols was similar in both cases. As previously noted with certain allylic alcohols, biphenyl formation was more pronounced for iodobenzene than bromobenzene.

In order to see how far the double bond would migrate along a carbon chain, we also examined the reaction of iodobenzene with 1-decen-10-ol. The crude reaction product contained aldehydes but these could not easily be separated from the complex mixture of alcohols which was also present.

For most of the examples given in Table II, a single carbonyl product predominated and was obtained in good yield. These results should not be generally extrapolated, however, since four of the alcohols used in Table II have the same structure about the double bond, a structure which favors terminal addition to the double bond. Further, using different experimental conditions, Heck and coworker have noted that aryl bromides can give rise to a higher ratio of unsaturated alcohols to carbonyl compounds than aryl iodides.[2] The possibility of changing reaction conditions to produce solely unsaturated alcohols is presently under study.

Experimental Section

Materials were obtained from commercial sources (aryl halides, Aldrich, Eastman; unsaturated alcohols, Chemical Samples). They were used without purification.

Procedures have been previously reported.[1] Products were isolated by distillation or by preparative GC (6 ft × 0.25 in. Carbowax 20M or SE-30) and identified by NMR, MS, and ir. A typical example follows.

3-(4′-Carboethoxyphenyl)-2-methylpropanal. Palladium acetate (0.30 g, 1.35 mmol) and triphenylphosphine (0.72 g, 2.7 mmol) were dissolved in 60 ml of hexamethylphosphoramide and sodium bicarbonate (15 g, 0.18 mol), 2-methyl-2-propen-1-ol (13.1 g, 0.18 mol), and ethyl 4-bromobenzoate (37.8 g, 0.16 mol) added. The mixture was heated to 130 °C under nitrogen. After 42 min the reaction was stopped and the mixture cooled when GC revealed 100% conversion of the aryl halide. The reaction mixture was then poured into 1 l. of water and extracted three times with 150-ml portions of toluene. The combined toluene extracts were then back extracted with 150 ml of water, evaporated to give 34.2 g of product, and distilled using a short-path still to give 25.8 g (71%) of product.

Supplementary Material Available. Full NMR data for the compounds synthesized (5 pages). Ordering information is given on any current masthead page.

Registry No.—2-Methyl-2-propen-1-ol, 513-42-8; 2-methyliodobenzene, 615-37-2; 4-methoxyiodobenzene, 696-62-8; 4-iodophenol, 540-38-5; 4-nitroiodobenzene, 636-98-6; 4-*tert*-butyliodobenzene, 35779-04-5; ethyl 4-bromobenzoate, 5798-75-4; 4-bromobenzaldehyde, 122-91-4; 4-bromobenzonitrile, 623-00-7; 4-bromoacetophenone, 99-90-1; 3,4-methylenedioxybromobenzene, 2635-13-4; 4-*tert*-butylbromobenzene, 3972-65-4; 4-isopropylbromobenzene, 586-61-8; 4-methoxybromobenzene, 104-92-7; 4-methylbromoben-

zene, 106-38-7; 3-methyl-1-buten-3-ol, 115-18-4; 1-buten-3-ol, 598-32-3; 3-buten-1-ol, 627-27-0; 4-penten-1-ol, 821-09-0; 3-methyl-3-buten-1-ol, 763-32-6; 5-methyl-5-hexen-2-ol, 50551-88-7; 4-methyl-4-penten-2-ol, 2004-67-3; 4-methyl-4-penten-1-ol, 22508-64-1; bromobenzene, 108-86-1; iodobenzene, 591-50-4; β-terpineol, 138-87-4; 1-methyl-3-cyclohexene-1-methanol, 50552-10-8.

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(2) R. F. Heck and J. B. Melpolder, *J. Org. Chem.*, **41**, 265 (1976).
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(4) J. M. Davidson and C. Triggs, *J. Chem. Soc. A*, 1324 (1968).

The Chemistry of Carbanions. XXVIII. The Carbon-13 Nuclear Magnetic Resonance Spectra of Metal Enolates[1]

Herbert O. House,* Ananth V. Prabhu, and William V. Phillips

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

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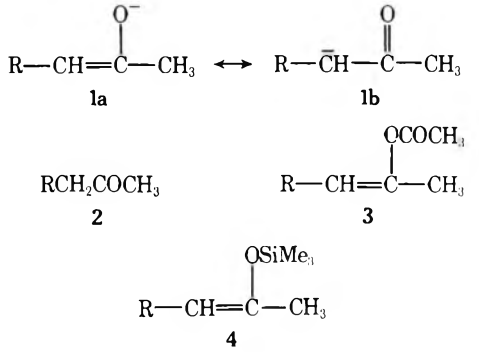
The natural abundance ^{13}C NMR spectra of several metal enolates **5–10** have been measured in various aprotic solvents including Et_2O, THF, and DME. The chemical shifts of the enolate α-carbon atoms are readily measured and have been compared with the chemical shifts of the same carbon atoms in the corresponding enol acetates **17–22** and trimethylsilyl enol ethers **23–26**. The observed chemical shift differences ($\Delta\delta$) between the enolates and the enol acetates appear to be related both to the π-electron density and the reactivity at the enolate α-carbon atom. The following changes increase the magnitude of the chemical shift differences (and presumably the π-electron charge density) in metal enolates: (1) changing the metal cation from Li^+ to Na^+ to K^+; (2) changing the solvent from Et_2O to THF to DME; (3) addition of 4 molar equiv of HMP to a Li^+ enolate; and (4) addition of 1 molar equiv of dicyclohexyl-18-crown-6 polyether to a Na^+ enolate. The magnitudes of the chemical shift differences at the enolate α-carbon atoms are relatively insensitive to the presence or absence of α-alkyl or α-phenyl substituents.

In an early study[2] of the properties and reactions of solutions of metal enolates **1** derived from ketones **2**, comparison of the ^{1}H NMR spectra for a related set of compounds **1–4** (R = Ph) showed that the vinyl H atom signal moved progressively upfield in the order enol acetate **3** (δ 5.80), trimethylsilyl enol ether **4** (δ 5.32), and lithium enolate **1** (δ



5.02 in Et_2O, 4.93 in THF, and 4.83 in DME). Among the various cations and solvents studied with this enolate system, the cation–solvent combinations that resulted in the greatest upfield shift of the vinyl H atom NMR signal were also the combinations that resulted in the greatest proportion of O- to C-acylation of the enolate anions and corresponded qualitatively to conditions that favored most rapid reaction of the enolate anion with alkylating agents. Thus, the location of the ^{1}H NMR signal appeared to offer a useful measure of the reactivity of a metal enolate under various reaction conditions. However, two experimental problems dissuaded us from further study of the ^{1}H NMR spectra of metal enolates. First, the total range of ^{1}H NMR values observed for a particular enolate system was rather small (ca. 0.3 ppm) so that changes in chemical shift arising from nearby anisotropic substituents were likely to be as large as chemical shift differences arising from changes in the degree of association and charge distribution of metal enolates. Even more troubling was the interference from the ^{1}H NMR signals of the various solvents (Et_2O, THF, DME, DMF, etc.) commonly used with metal enolates.

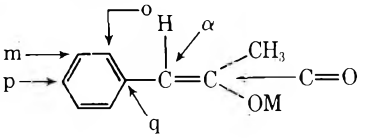
It appeared that both of these problems could be largely alleviated by studying the natural abundance ^{13}C NMR spectra of metal enolate solutions. Because of the much larger range of chemical shift values in ^{13}C NMR and the relatively narrow linewidths obtainable, problems arising from interference between solvent peaks and peaks from the metal enolates would be more easily avoided. Of equal importance is the fact that electron densities at carbon and the atoms bonded to it, but not shielding from neighboring anisotropic substituents, are dominant in determining ^{13}C NMR chemical shift values.[3]

To explore this possibility, a series of metal enolates **5–10** (Scheme I) of ketones **11–16** were prepared. Also included in the study were the corresponding enol acetates **17–22** as well as selected enol silyl ethers **23–26**, one enamine **27**, and the sodium enolate **28** of diethyl malonate.

Although relatively high concentrations (0.5–1.0 M) of metal enolates in solution were required in order to obtain satisfactory natural abundance ^{13}C NMR spectra in a reasonable period of time (1–3 h), we were gratified to find that interference between ^{13}C NMR signals for the metal enolates and the solvents was much less of a problem than had been encountered in measurements of ^{1}H NMR spectra of metal enolates.[2] Consequently, where solubility permitted, satisfactory ^{13}C NMR spectra of various metal enolates could be obtained in most common solvents used in preparative work including Et_2O, THF, DME, DMF, and HMP. The data obtained from these measurements are summarized in Tables I and II. In one case (enolate **5a** in DME, Table I) we demonstrated that the chemical shift values were essentially the same for 1.0 and 0.2 M solutions of the enolate. Because of the time required to obtain satisfactory ^{13}C NMR spectra of dilute solutions, it was not practical to collect data for enolate solutions less concentrated than 0.2 M.

In order to compare the ^{13}C NMR data for various metal enolates, we elected to relate the enolate chemical shift

Table I. ^{13}C NMR Data for Phenylacetone Derivatives



Compd (solvent)	Position of ^{13}C NMR signals, ppm relative to Me_4Si						
	p	o and m positions		q	α ($\Delta\delta$)[a]	C=O	CH_3 and other C atoms
$PhCH_2COCH_3$ 11 (DME)	127.2	129.5	129.5	135.7	50.9	204.3	28.8
$PhCH{=}C(CH_3)OCOCH_3$ 17 (DME)	127.5	128.9	128.9	135.4	116.6[c]	147.0	168.0, 20.6[b]
$PhCH{=}C(CH_3)OSi(CH_3)_3$ 23 (DME)	125.1	127.7	127.7	137.1	108.7 (7.9)	148.8	23.8, 0.8
$PhCH{=}C(CH_3)OK$ 5c (DME)	118.6	123.3	128.4	145.6	91.8 (24.8)	170.7	29.5
$PhCH{=}C(CH_3)ONa$ 5b (DME)	119.2	124.1	128.2	145.1	93.4 (23.2)	169.3	29.4
5b (DME + 1.0 equiv of crown ether 35)[d]	116.4	123.1	126.7	146.0	90.7[e] (25.9)	170.3	29.7
$PhCH{=}C(CH_3)OLi$[f] 5a (DME)	120.0	125.0	127.2	143.2	95.3 (21.3)	164.7	28.6
5a (DME + 4.1 equiv of HMP)	117.7	124.1	126.6	144.8	93.1 (23.5)	167.4	28.9
5a (THF)	120.9	125.5	127.5	141.8	97.1 (19.5)	162.5	28.6
5a (THF + 3.9 equiv of HMP)	118.9	124.7	127.6	144.0	94.4 (22.2)	166.0	28.7
5a (Et_2O)	122.3	125.8	128.4	142.1	97.8[g] (18.8)	160.6	27.1
5a (Et_2O + 5.1 equiv of HMP)	118.5	124.6	127.0	144.3	94.1 (22.5)	166.4	28.6
5a (THF + 0.9 equiv of crown ether 36)	120.5	125.1	127.5	142.5	96.4 (20.2)	163.7	28.7
5a (THF + 1.1 equiv of crown ether 37)	120.5	125.1	127.6	142.5	96.5 (20.1)	163.9	28.8

[a] $\Delta\delta$ is the difference in chemical shift between the α-carbon atom of the enol acetate and the α-carbon atom of the enolate or trimethylsilyl enol ether. [b] The signals for both CH_3 groups are superimposed. [c] The $^1J_{CH}$ value was 154 ± 3 Hz. [d] Within experimental error, the same ^{13}C chemical shift values were obtained with a solution containing 2 molar equiv of the crown ether 35. [e] The $^1J_{CH}$ value was 146 ± 3 Hz. [f] The values listed were obtained with a 1.0 M solution of the enolate 5a. For a 0.2 M solution of the same enolate, the values follow: 120.0, 125.0, 127.4, 143.3, 95.3, 164.8, and 28.6 ppm. [g] The $^1J_{CH}$ value was 154 ± 3 Hz.

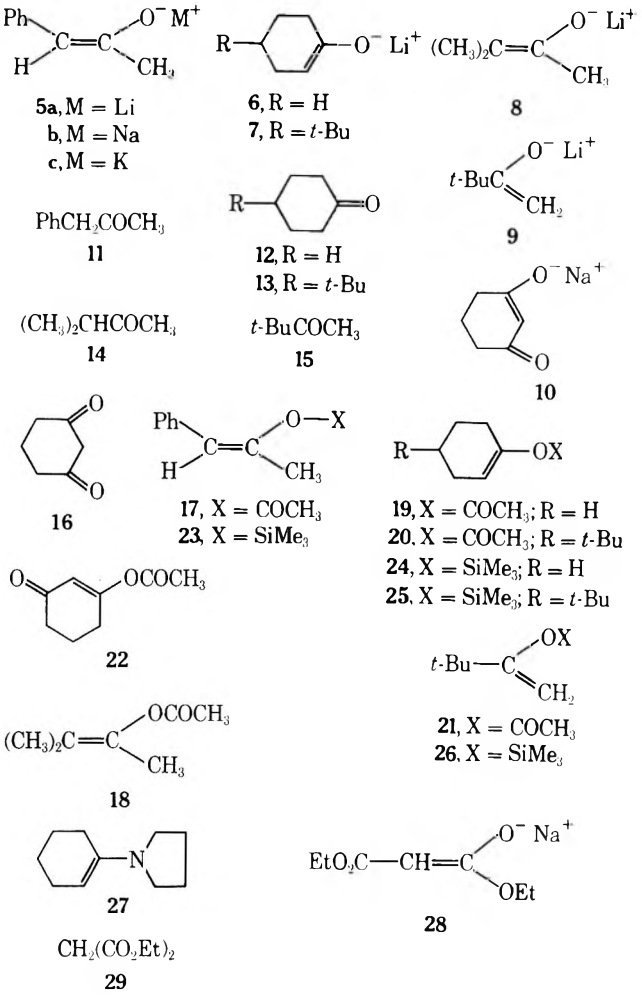
data to the analogous data for the corresponding enol acetates,[4] which can serve as neutral model compounds with geometries and substituent patterns similar to those of the metal enolates. This comparison utilizes the ^{13}C NMR shift difference ($\Delta\delta = \delta_{\text{enol acetate}} - \delta_{\text{enolate}}$) between the α-carbon atom in a metal enolate and the corresponding carbon atom in the related enol acetate. It will be seen from Tables I and II that $\Delta\delta$ values for the α-carbon atom of monoketone enolates are in the range +19 to +25 ppm. This upfield shift of signal for the α-carbon atom in the metal enolate is accompanied by a downfield shift of −13 to −23 ppm for the "carbonyl carbon atom" of the metal enolate. In general, the largest upfield shifts of α-carbon atoms are accompanied by the largest downfield shifts of the enolate "carbonyl carbon atoms".

One of the factors responsible for an upfield shift of the ^{13}C NMR signal for an sp^2 carbon atom[2] (or a hydrogen atom bound to this carbon[5]) is an increase in the π-electron density at carbon. From studies of various hydrocarbons and the related ions, it has been suggested that an increase by one unit of negative charge in the p orbital of such a carbon atom should result in an upfield shift of 150–160 ppm for the ^{13}C NMR signal[6] and an upfield shift of ca. 10 ppm for the ^1H NMR signal of a proton bound to such a carbon atom.[5a,7] As examples of this upfield shift in hydrocarbons, the α-carbon atoms and the C-4 carbon atoms of the phenyl groups in DME solutions of the organolithium reagents **30** and **31** (Scheme II) exhibit ^{13}C NMR signals at 14–71 ppm higher field than the analogous neutral olefin **32**[8,9] and the ^{13}C NMR signal for the cyclopentadienide anion **33** (in THF) is at 25 ppm higher field than the corresponding signal for benzene (**34**).

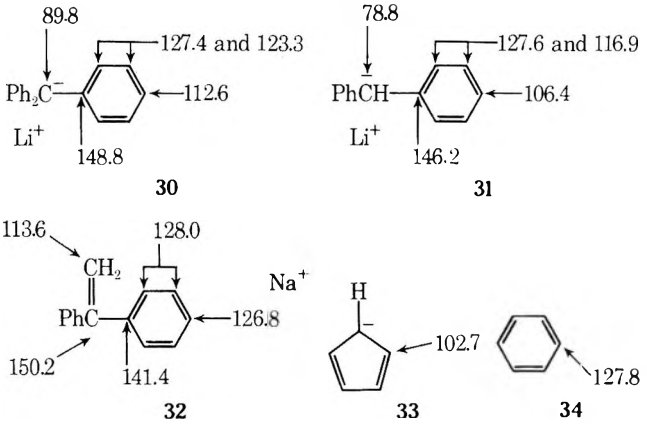
The aforementioned upfield shift differences (0.7–1.9 ppm for α-H atoms and 19–25 ppm for α-C atoms) observed when metal enolates are compared with the analogous enol acetates would suggest that the π-electron density at the α-C atom is greater in the metal enolates than in enol acetates by approximately 12–17% of a unit negative charge. Since there is question as to the quantitative relationship between ^{13}C chemical shift differences and calculated charge densities, especially in ionic molecules and in molecules containing heteroatoms,[3,10] it appears prudent to discuss the properties of various metal enolates in terms of the measured chemical shift difference parameter $\Delta\delta$ rather than calculated charge densities. However, it is appropriate to note that this parameter $\Delta\delta$ does appear to be largest in those circumstances where the enolate anions **1** might be expected to have a significant contribution from structure **1b** with the negative charge concentrated at the α-carbon atom.

In two cases, enolates **5a** and **6**, we measured the coupling constants, $^1J_{CH}$, between the α-carbon atom and the attached proton. The J values obtained, 145–154 Hz, did not differ appreciably from the J values, 154–157 Hz, for

Scheme I



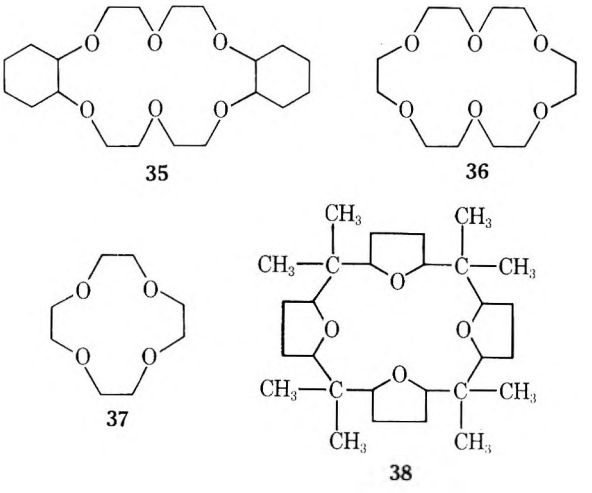
Scheme II. ^{13}C NMR Data



the corresponding enol acetates **11** and **19**. Consequently, these measurements suggest that the α-carbon atom of these enolates is not deformed significantly from a planar sp^2 configuration.

The high order of reactivity observed[11] in reactions of potassium enolates with alkyl halides is compatible with the $\Delta\delta$ values observed. In DME solution, the $\Delta\delta$ values decrease regularly in progressing from the K enolate **5c** ($\Delta\delta$ 24.8) to the Na enolate **5b** ($\Delta\delta$ 23.2) to the Li enolate **5a** ($\Delta\delta$ 21.3). The enhanced rate of alkylation of lithium enolates obtained by use of DME rather than Et_2O as a reaction solvent[12] is also consistent with the $\Delta\delta$ values observed. For the Li enolate **5a**, the $\Delta\delta$ values change with solvent as follows: DME ($\Delta\delta$ 21.3), THF ($\Delta\delta$ 19.5), Et_2O ($\Delta\delta$ 18.8). The addition of 4 equiv [sufficient to form the tetracoordinate solvated cation, $Li(HMP)_4^+$] of HMP, a solvent believed to be one of the most effective for solvation of metal cations,[13] to solutions of the lithium enolate **5a** in Et_2O, THF, or DME increased the values of $\Delta\delta$ to 22.5, 22.2, and 23.5 ppm, respectively. The largest effect (increasing $\Delta\delta$ by 3.7 ppm) was observed in adding 4 equiv of HMP to an Et_2O solution of the Li enolate. This observation is consistent with the practice of adding HMP to an Et_2O solution of a lithium enolate in order to increase its rate of reaction with an alkyl halide.[14]

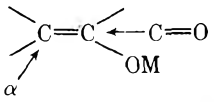
Interestingly, the most effective additive for increasing the $\Delta\delta$ value at the α carbon of the enolate **5** (to $\Delta\delta$ 25.9) was the addition of 1 molar equiv of the crown ether **35** to a solution of the Na enolate **5b** in DME. Since no further change in the chemical shift values of enolate **5b** was observed when a second molar equivalent of the crown ether **35** was added, the formation of a 1:1 Na^+ cation–crown ether **35** complex is evidently very favorable. Unfortunately, we were unable to obtain sufficiently concentrated solutions of the K enolate **5c** in the presence of 1 molar equiv of either of the crown ethers **35** or **36** to permit NMR measurements.

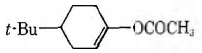
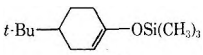
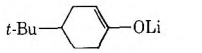
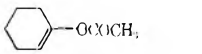
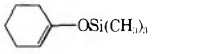
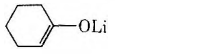
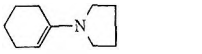
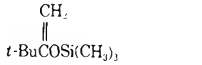
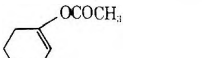
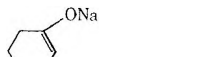
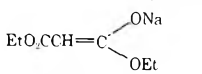


In contrast to the results obtained with the sodium enolate **5b**, the addition of 1 molar equiv of either of the crown ethers **36** or **37** to THF solutions of the lithium enolate **5a** had relatively little effect on the chemical shift values. Consequently, it appears that neither of the crown ethers **36** or **37** forms a sufficiently stable complex with Li^+ cation to enhance significantly the reactivity of lithium enolates. Since the common synthetically useful methods for the regiospecific generation of metal enolates produce lithium enolates, it is clearly desirable to find a crown ether of proper geometry to form a very stable complex with Li^+ cation, and we plan to continue our search for a suitable additive. Unfortunately, the low solubility of the crown ether **37** in ethereal solvents prevented us from obtaining useful ^{13}C NMR data in the presence of this material. It should be noted that the type of ^{13}C NMR measurements described in this paper do offer a rather simple experimental method for evaluating efficacy of various polydentate ligands as additives to enhance the reactivity of metal enolates.

It was also of interest to compare the $\Delta\delta$ values for the terminal lithium enolate **9** with the corresponding values for enolates **6–8** in which alkyl substituents are present at the α-carbon atom. Earlier work[15] had suggested that metal enolates with no alkyl substituents at the α-carbon atom are *less reactive* than analogous metal enolates with α-alkyl substituents. The $\Delta\delta$ values for DME solutions of

Table II. ^{13}C NMR Data for Saturated Carbonyl Derivatives



Compd (solvent)	Position of ^{13}C NMR signals, ppm relative to Me_4Si		
	α (Δδ)[a]	C=O	Other C atoms[b]
$(CH_3)_2CHCOCH_3$ 14 (DME)	41.7	210.0	18.3 (2 CH_3), 27.1 (acetyl CH_3)
$(CH_3)_2C{=}C(CH_3)OCOCH_3$ 18 (DME)	117.8	139.8	16.0 (CH_3), 17.3 (CH_3), 18.6 (CH_3), 20.3 (acetyl CH_3), 168.4 (ester C=O)
$(CH_3)_2C{=}C(CH_3)OLi$ 8 (DME)	92.3 (25.5)	150.6	18.7 (CH_3), 20.4 (CH_3), 21.5 (CH_3)
 20 (DME)	113.0	148.4	20.5 (acetyl CH_3), 27.4 (3 CH_3 of *t*-Bu group), 24.5 (CH_2), 25.4 (CH_2), 28.3 (CH_2), 44.0 (CH at C–4), 32.3 (C of *t*-Bu group), 167.6 (ester C=O)
 25 (DME)	102.5 (10.5)	149.7	0.0 (3 CH_3 of Me_3Si group), 27.0 (3 CH_3 of *t*-Bu group), 24.4 (CH_2), 25.0 (CH_2), 30.9 (CH_2), 44.0 (CH at C–4), 31.9 (C of *t*-Bu group)
 7 (DME)	91.5 (21.5)	158.4	27.7 (3 CH_3 of *t*-Bu group), 25.9 (CH_2), 26.5 (CH_2), 34.5 (CH_2), 45.7 (CH at C–4), and 32.5 (C of *t*-Bu group)
 19 (DME)	113.2[c]	148.5	20.5 (acetyl CH_3), 22.3 (CH_2), 23.2 (CH_2), 24.0 (CH_2), 27.3 (CH_2), 167.8 (ester C=O)
 24 (DME)	102.8 (10.4)	149.9	0.3 (3 CH_3 of Me_3Si group), 22.6 (CH_2), 23.3 (CH_2), 23.8 (CH_2), 30.0 (CH_2).
 6 (DME)	91.7[d] (21.5)	158.6	24.5 (CH_2), 25.0 (CH_2), 25.5 (CH_2), 33.7 (CH_2)
6 (THF)	89.6 (23.6)	159.0	25.0 (CH_2), 25.6 (CH_2), 26.1 (CH_2), 33.9 (CH_2)
 27 (DME)	93.0 (20.2)	142.5	23.7 (CH_2), 24.0 (CH_2), 24.9 (3 CH_2, cyclohexenyl CH_2 and 2 CH_2 at β position of pyrrolidine), 47.4 (2 CH_2 at α position of pyrrolidine)
t-$BuCOCH_3$ 15 (DME)	24.1	210.3	26.4 (3 CH_3 of *t*-Bu group), 44.0 (C of *t*-Bu group)
t-$BuC(OCOCH_3){=}CH_2$ 21 (DME)	98.4	162.2	20.6 (acetyl CH_3), 27.9 (3 CH_3 of *t*-Bu group), 36.3 (C of *t*-Bu group) 167.3 (ester C=O)
 26 (DME)	85.5 (12.9)	166.5	0.1 (3 CH_3 of Me_3Si group), 28.2 (3 CH_3 of *t*-Bu group) 36.6 (C of *t*-Bu group)
t-$BuC(OLi){=}CH_2$ 9 (DME)	73.5 (24.9)	176.8	29.7 (3 CH_3 of *t*-Bu group), 37.5 (C of *t*-Bu group)
 22 (DME)	117.1	169.1	20.7 (acetyl CH_3), 21.7 (CH_2), 28.3 (CH_2), 36.9 (CH_2), 166.8 (ester C=O), 197.1 (ketone C=O)
22 (DMF)	116.7	169.6	20.9 (acetyl CH_3), 21.5 (CH_2), 28.5 (CH_2), 36.8 (CH_2), 167.7 (ester C=O), 197.7 (ketone C=O)
 10 (DMF)	102.3 (14.4)	193.5	22.9 (CH_2 at C–5), 36.6 (2 CH_2 at C–4 and C–6)
$CH_2(CO_2Et)_2$ 29 (DMF)	41.6	166.1	14.1 (2 CH_3 of ethoxyl groups), 61.0 (2 CH_2 of ethoxyl groups)
 28 (DMF)	62.1[e]	171.4	15.3 (2 CH_3 of ethoxyl groups) 56.1 (2 CH_2 of ethoxyl groups)

[a] Δδ is the chemical shift difference between the α-carbon atom of the enol acetate and the α-carbon atom of the enolate or related derivative. [b] Unless otherwise noted, each ^{13}C signal corresponds to a single carbon atom. [c] The $^1J_{CH}$ value was 157 ± 3 Hz. [d] The $^1J_{CH}$ value was 145 ± 3 Hz. [e] Since we lacked a suitable model, no measure of Δδ was made.

the unsubstituted enolate **9** ($\Delta\delta$ 24.9) and the enolate **8** ($\Delta\delta$ 25.5) with two methyl substituents are practically the same and both are greater than the values observed for the cyclohexanone enolates **6** ($\Delta\delta$ 21.5) and **7** ($\Delta\delta$ 21.5). Even in the case of a DME solution of the Li enolate **5a**, where some delocalization of negative charge into the para position of the phenyl ring was evident, the $\Delta\delta$ value (21.3) was comparable to the values observed with the cyclohexanone enolates **6** and **7**. Only in the case of the β-diketone enolate **10**, where delocalization of the negative charge to two equivalent carbonyl groups was possible, did the $\Delta\delta$ value (14.4) decrease. The decreased value of $\Delta\delta$ (presumably corresponding to diminished charge density at the enolate α-carbon atom) is compatible with the general observation that enolates of β-diketones tend to give significant amounts of *O*-alkyl products upon reaction with alkylating agents.

The several trimethylsilyl enol ethers **23**, **25**, **24**, and **26** examined had $\Delta\delta$ values (7.9–12.9) approximately half as large as the values observed for the metal enolates, an observation consistent with the fact that these materials are significantly poorer nucleophiles than metal enolates. Interestingly, the $\Delta\delta$ value (20.2) for the one enamine **27** examined was practically the same as the value for the corresponding metal enolate.

In conclusion, the $\Delta\delta$ values observed with a particular enolate system do appear to vary in a systematic way with changes in the metal cation, the solvent, and added ligands that can coordinate with the metal cation. In general, those combinations of cation, solvent, and added ligands that give the largest value of $\Delta\delta$ are also the combinations that result in the highest reactivity of the enolate with alkyl halides and in the greatest proportion of O- to C-acylation in reaction with Ac_2O. However, comparison of $\Delta\delta$ values for structurally different enolates derived from monoketones has not revealed any obvious relationship between the substitution pattern of the enolate anion, its reactivity, and its $\Delta\delta$ value.

Experimental Section[16]

Reagents and Starting Materials. All ethereal solvents were distilled from $LiAlH_4$ immediately before use. Previously described purification procedures[17] were used for Me_2NCHO (DMF) and $(Me_2N)_3PO$ (HMP). Oil dispersions (Alfa Inorganics) of NaH and KH were washed free of oil with purified pentane immediately before use. Ethereal solutions of halide-free MeLi (Foote Mineral Co.) were standardized by previously described procedures.[18] Samples of the trans enol acetate **17** and the trans silyl enol ether **23** were obtained by the previously described[2,19] reactions of the trans enolate **5b** with Ac_2O or Me_3SiCl. Previously described procedures were also used to obtain the silyl enol ethers **24**,[19a] **25**,[19a] and **26**[19a] and the enol acetates **19**,[2] **20**,[19b] and **21**.[19c] Reaction of dihydroresorcinol with excess boiling Ac_2O as previously described[20] produced the enol acetate **22** in 80% yield as a colorless liquid: bp 96 °C (0.8 mm); $n^{25}D$ 1.4916 [lit.[20] bp 117 °C (6 mm)]; ir (CCl_4) 1773 (enol ester C=O), 1680 (conjugated C=O), and 1642 cm^{-1} (C=C); NMR (CCl_4) δ 5.6–5.7 (1 H, m, vinyl CH) and 1.7–2.7 (9 H, m, aliphatic CH including a CH_3CO singlet at 2.15); mass spectrum *m/e* (rel intensity), 154 (M^+, 12), 112 (15), 84 (56), 69 (12), and 43 (100).

Preparation of the Enol Acetate 18. To a solution of 200 g (2.0 mol) of Ac_2O and 34.4 g (0.40 mol) of *i*-PrCOMe in 450 ml of CCl_4 was added 0.28 ml of aqueous 70% $HClO_4$. After the resulting solution had been allowed to stand overnight, it was partitioned between 300 ml of pentane and 320 ml of saturated aqueous $NaHCO_3$. The organic layer was stirred over cold (0–8 °C) saturated aqueous $NaHCO_3$ to which was added portionwise 300 g of solid $NaHCO_3$ to complete the hydrolysis of Ac_2O. The combined organic layer and pentane extract of the aqueous phase were washed successively with H_2O, aqueous $NaHCO_3$, and aqueous NaCl and then dried (Na_2SO_4) and concentrated by fractional distillation. Fractional distillation of the residual liquid separated 9.0 g of material, bp 110–115 °C $n^{25}D$ 1.4370, containing (GLC, TCEP on Chromosorb P) ca. 80% of the enol acetate **18** (retention time 5.3 min) accompanied by CCl_4 (1.3 min) and the starting ketone (2.7 min) and 16.54 g of material, bp 116–125 °C, $n^{25}D$ 1.4230 [lit.[21] bp 121 °C (763 mm), $n^{20}D$ 1.4222], containing (GLC) >98% of the enol acetate **18**: ir (CCl_4) 1755 (enol ester C=O) and 1701 cm^{-1} (enol C=C); NMR (CCl_4) δ 2.03 (3 H, s, $COCH_3$) with three partially resolved multiplets at 1.81, 1.70, and 1.51 (each 3 H, allylic CH_3); mass spectrum *m/e* (rel intensity) 128 (M^+, 66), 87 (17), 86 (79), 85 (18), 71 (100), 58 (22), 43 (89), 41 (46), and 39 (27).

Preparation of Solutions for NMR Study. A. Ph_3CLi and Ph_2CHLi. Solutions of ca. 23 mmol of MeLi in 8 ml of DME were prepared by a previously described procedure[18b] in which Et_2O solutions of MeLi were concentrated under reduced pressure and the residual solid MeLi (still containing some Et_2O) was redissolved in DME. These solutions were treated with 2–3 ml of a DME solution containing either 2.44 g (10 mmol) of Ph_3CH or 1.67 g (10 mmol) of Ph_2CH_2 and the resulting solutions were stirred for 30–90 min at 25 °C at which time ^1H NMR analysis indicated that conversion of the hydrocarbons to their lithio derivatives was complete and some excess MeLi remained in the solutions. Aliquots (3.0 ml) of these red (Ph_3CLi) or orange (Ph_2CHLi) solutions were mixed with 0.3 ml of C_6D_6 (to provide a "lock" signal) and 0.3 ml of Me_4Si (internal reference signal). The ^{13}C NMR spectra of these solutions and all subsequently described solutions were determined both with complete proton decoupling and with partial (off-resonance) proton decoupling. The "extraneous" ^{13}C NMR signals (from solvents and reagents) found in these and subsequently described solutions were found at the following locations (in parts per million relative to internal Me_4Si): C_6D_6, 126.9, 127.8, and 128.8; DME, 58.5 and 72.1; Et_2O, 15.5 and 65.8; THF, 26.1 and 67.8; MeLi, −14.0; DMF, 30.8, 35.8, and 161.9; $CDCl_3$, 75.3, 76.6, and 77.8; *t*-BuOLi (in DME), 35.6 and 66.4; *t*-BuOH (in DME), 31.4 and 67.8. In certain cases involving subsequently described solutions of enol acetates and metal enolates, the ^{13}C NMR spectra were measured without proton decoupling to obtain the coupling constant, $^1J_{CH}$, for the α carbon of the enol acetate or metal enolate. These $^1J_{CH}$ values are indicated in Tables I and II.

B. Olefins, Ketones, Enol Acetates, and Trimethylsilyl Enol Ethers. Solutions of these materials were prepared by dissolving 200–500 mg of each purified material in 2.5–3.0 ml of the solvent indicated in the tables and then adding 0.3 ml of C_6D_6 and 0.3 ml of Me_4Si.

C. Sodium and Potassium Enolates. A slurry of excess prewashed KH or NaH (1–2 mmol/ml of solvent) in the solvent stated in the tables was treated with one of the active methylene compounds **11**, **16**, or **29** and the mixture was stirred at 15–25 °C until H_2 evolution ceased (typically 20–30 min). Aliquots of these solutions were mixed with 10% (by volume) of C_6D_6 and 10% (by volume) of Me_4Si for ^{13}C NMR measurements. The ^1H NMR spectra of the phenylacetone enolates **5** were described previously.[2] A 1 M solution of the Na enolate **10** in DMF exhibited NMR signals at δ 4.49 (s, vinyl CH) and 1.1–2.5 (m, aliphatic CH).

D. Lithium Enolates. A 1.1 M solution of the Li enolate **8** (accompanied by *t*-BuOLi) in DME was obtained by reaction of the enol acetate **18** with a DME solution of MeLi in the usual manner.[18b] Solutions containing about 1 M Li enolate **5a** in Et_2O, THF, and DME were obtained by reaction of the trimethylsilyl enol ether **23** with excess MeLi in the appropriate solvent at 25 °C for 60 min. Aliquots of these solutions containing 2 mmol of the enolate **5a** in 2 ml of solvent were also either diluted with DME or treated with 1.4 ml (8 mmol) of freshly purified HMP before measurement of the ^{13}C spectra. Solutions containing 1 M Li enolate **6** or **9** in THF or DME were obtained by reaction of the corresponding trimethylsilyl enol ether **24** or **26** with MeLi. The Li enolate **6** was not sufficiently soluble in Et_2O to permit satisfactory NMR study. A 1 M solution of the Li enolate **7** in DME was similarly prepared by reaction of the trimethylsilyl enol ether **25** with MeLi.

E. $Na^+C_5H_5^-$. Freshly prepared cyclopentadiene (124 ml, 1.65 mol) was added dropwise and with stirring at 25 °C during 1.5 h to a suspension of 69.0 g (1.5 g-atom) of Na dispersion (50% in mineral oil) in 600 ml of DME.[22] After the addition was complete the white slurry was heated to reflux with stirring and then allowed to cool. The white to pale-pink crystalline $C_5H_5^-Na(DME)^+$ was separated from the red supernatant liquid, washed with hexane, and dissolved in THF to give a solution containing[18a] 0.80 M $C_5H_5^-Na^+$ as well as the DME present in the original complex. This solution (with added Me_4Si) exhibited a ^1H NMR singlet at δ 5.59; after addition of C_6D_6 and Me_4Si, the ^{13}C NMR spectrum exhibited a signal attributable to the $C_5H_5^-$ anion at 102.7 ppm.

F. Metal Enolates in the Presence of Crown Ethers. The dicyclohexyl crown ether **35** (mp 41–55 °C, lit.[23] mp 38–54 °C, a mix-

ture of the cis-syn-cis and cis-anti-cis stereoisomers) was prepared by a previously described procedure[23] as was the crown ether **38** (mp 203–206.5 °C, lit.[24] mp 208–211 °C, a mixture of stereoisomers).[24] Preparative procedures for the crown ethers **36** and **37** have been described elsewhere.[25] Solutions of the crown ethers **35–37** in DME (containing C_6D_6 and Me_4Si) exhibited the following ^{13}C NMR signals: **37,** 71.1 ppm; **36,** 70.9 ppm; **35,** 77.8 (CH–O), 71.2 (CH_2–O), 68.8 (CH_2–O), 28.4 (CH_2), and 22.6 ppm (CH_2). The polyether **38** was too insoluble in the ethereal solvents employed in this study to obtain useful ^{13}C NMR data.

Our efforts to study the ^{13}C NMR spectra of mixtures of the potassium enolate **5c** and a crown ether were unsuccessful because addition of 1 molar equiv of either of the crown ethers **35** or **36** to a DME solution of the potassium enolate **5c** resulted in the immediate separation of a precipitate. This precipitate from **5c** and **36** was also insoluble in Et_2O and in DMF. After a slurry of 468 mg (19.5 mmol) of NaH (prewashed with pentane) in 9 ml of DME containing 3.00 g (8.0 mmol) of crown ether **35** had been stirred at 25 °C for 15 min, 1.07 g (8.0 mmol) of ketone **11** was added, dropwise and with stirring. The mixture was stirred until H_2 evolution ceased to give a dark red solution of the enolate **5b** containing 1 molar equiv of crown ether **35.** A comparable procedure was used to obtain a DME solution of the enolate **5b** containing 2 molar equiv of crown ether **35.** Aliquots (2.00 ml) of these solutions were mixed with 0.25 ml of C_6D_6 and 0.25 ml of Me_4Si to obtain the ^{13}C NMR data listed in Table I. The ^1H NMR spectrum of this solution exhibited a singlet at δ 4.60 attributable to the enolate vinyl CH; the corresponding signal for a solution of this enolate **5b** in DME with no added crown ether is at δ 4.70.[2]

A 3-ml aliquot of a solution of the enolate **5a,** prepared from 1.265 g (6.14 mmol) of the silyl enol ether **23** and 8.8 mmol of MeLi in 6 ml of THF, was mixed with 750 mg (2.8 mol, 0.9 molar equiv) of the crown ether **36** in 1.2 ml of THF containing 0.35 ml of C_6D_6 and 0.25 ml of Me_4Si for NMR study. Similarly, a solution for NMR study was prepared from 1.0 ml of a THF solution containing 1.12 mmol of the lithium enolate **5a,** 1.2 mmol (1.1 molar equiv) of the crown ether **37** (dried over LiH), 0.25 ml of C_6D_6, and 0.15 ml of Me_4Si.

Registry No.—**5a,** 37392-64-6; **5b,** 37392-66-8; **5c,** 57918-71-5; **6,** 21300-30-1; **7,** 20826-82-8; **8,** 57918-72-6; **9,** 34865-75-3; **10,** 57910-97-1; **11,** 103-79-7; **14,** 563-80-4; **15,** 75-97-8; **17,** 19980-46-2; **18,** 3814-41-3; **19,** 1424-22-2; **20,** 7360-39-6; **21,** 3840-71-9; **22,** 57918-73-7; **23,** 19980-24-6; **24,** 6651-36-1; **25,** 19980-19-9; **26,** 17510-46-2; **27,** 1125-99-1; **28,** 57918-74-8; **29,** 105-53-3; **30,** 733-90-4; **31,** 881-42-5; *cis-syn-cis*-**35,** 15128-65-1; *cis-anti-cis*-**35,** 15128-66-2; **36,** 17455-13-9; **37,** 294-93-9; acetic anhydride, 108-24-7.

References and Notes

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(9) In a private communication, Professor Daniel H. O'Brien has suggested that the differences between the ^{13}C NMR values we observed for the lithium compounds **30** and **31** in DME solution and the values he observed (ref 6e) for the analogous potassium derivatives in THF is attributable to the existence of the Li derivatives in DME as solvent separated ions and the K derivatives in THF as contact ion pairs.

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Carbon-13 Chemical Shifts of 1-Substituted Norbornanes

Graham S. Poindexter and Paul J. Kropp*[1]

Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514

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^{13}C chemical shifts for 12 monosubstituted 1-norbornanes are reported and the substituent effects compared with those of 1-substituted adamantanes and bicyclo[2.2.2]octanes. Except for an anisotropy effect exhibited by phenyl, β- and γ-substituent effects correlate reasonably well in the three systems and appear to operate principally via a through-bond effect. Surprisingly, α-substituent effects are apparently sensitive to the degree of strain at C-1 and do not correlate well in the three systems. The δ-substituent effects at C-4 of the 1-norbornyl system correlate with those of the 1-bicyclo[2.2.2]octyl system, but not those of the 1-adamantyl system, apparently because of either a strong 1,4 field effect or an α,γ-hyperconjugative effect in the former systems.

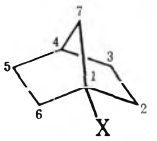
Conformationally rigid bicyclic and tricyclic systems have been quite useful in the study of substituent effects in ^{13}C spectroscopy. Because of the well-defined molecular frameworks, it has been possible, at least qualitatively, to partition some of the factors contributing to substituent effects in such systems (geometric, inductive, field, and steric effects[2]), and to assess their relative importance. Investigations have been conducted on norbornane,[3-6] bicyclo[2.2.2]octane,[5,7] adamantane,[8,9] nortricyclene,[10] and tricyclene systems.[11] However, except for studies involving bridgehead-substituted derivatives of these systems, uncertainties exist with regard to some of the chemical shift assignments, which were based on the premise that steric crowding results in upfield shifts, an assumption which is now open to question.[12] Assignments are more straightforward in bridgehead-substituted systems. Although 1-substituted adamantanes,[8,9] bicyclo[2.2.2]octanes,[7] and tricyclenes[11] have been studied extensively, their norbornyl analogues have not received attention except for the 1-methyl derivative.[3,4] It is of particular interest to examine chemical shifts in the 1-norbornyl system, which is substantially more strained than the adamantyl and bicyclo[2.2.2]octyl systems.

In the norbornyl system the carbon atoms γ to a C-1 substituent (i.e., C-3, -4, and -5) are essentially antiperiplanar with respect to the substituted carbon and have no nonbonded interactions with the substituent. This can be seen in Figure 1, which depicts Newman projections of the γ carbons with respect to the 1,7 and 1,2 carbon–carbon bonds. C-4 is conformationally locked in a true antiperiplanar arrangement with the substituent while C-3 and -5 are in a "skewed" antiperiplanar arrangement with the angle between C-3 or -5 and the substituent being somewhat less than 180°. Moreover, the absence of long-range nonbonded interactions leaves the substituted norbornane nucleus sterically unperturbed compared to that of the unsubstituted norbornane.[15] Hence, 1-substituted norbornanes, as with 1-substituted bicyclo[2.2.2]octanes and adamantanes, are excellent systems in which to isolate and study ^{13}C through-bond and field effects.

Results

Assignments were made on the basis of relative signal intensities and verified by the proton-induced splitting in the off-resonance decoupled spectra of norbornanes **2**, **4**, and **9**. The most intense peaks were assigned to the doubly degenerate carbons C-2,6 and C-3,5. The remaining three signals in order of decreasing intensity (presumably due to increased relaxation time) were assigned to C-7, -4, and -1, which bear two, one, and no hydrogen substituents, respectively.

The off-resonance decoupled spectra of 1-chloro- (2) and 1-iodonorbornane (4) and 1-norbornanecarboxylic acid (9)



1, X = H
2, X = Cl
3, X = Br
4, X = I
5, X = OH
6, X = OCH_3
7, X = OC_2H_5
8, X = CH_3
9, X = CO_2H
10, X = CO_2CH_3
11, X = C_6H_5
12, X = *o*-$C_6H_4CH_3$
13, X = $NHCOCH_3$

confirmed these assignments through the following observed multiplicities: C-1, singlet; C-2,6, multiplet;[16] C-3,5, multiplet;[16] C-4, doublet; and C-7, triplet. C-2,6 and -3,5 were differentiated on the basis of relative substituent shifts compared to 1-chlorobicyclo[2.2.2]octane, whose signals have been unequivocally assigned.[7]

The ^{13}C chemical shifts for 1-substituted norbornanes and the corresponding substituent effects are listed in Tables I and II, respectively. No large shift discrepancies were noted compared to known substituent effects of bicyclic compounds. The ^{13}C chemical shifts of 1-methylnorbornane have been reported previously.[3,4] Our absolute chemical shifts for the methyl derivative are consistently 0.4 ppm upfield of those of Roberts,[3] and our substituent effects are in complete agreement with his. However, our results are at

Table I. ^{13}C Chemical Shifts of 1-Substituted Norbornanes[a]

X	C-1	C-2,6	C-3,5	C-4	C-7	C-1′	C-2′
H	36.4	29.8	29.8	36.4	38.4		
Cl	69.9	38.4	30.9	34.8	46.8		
Br[b]	62.2	40.0	31.6	34.8	48.2		
I	37.7	43.0	32.1	34.6	50.8		
OH	82.8	35.4	30.3	34.8	43.9		
OCH_3[b]	87.7	31.0	29.9	33.9	40.0	52.7	
OC_2H_5[b]	87.1	31.7	30.0	33.8	40.7	60.3	16.1
CH_3[b]	43.7	36.7	31.2	37.8	45.2	20.9	
CO_2H	52.1	32.9	30.0	37.8	42.3	183.5	
CO_2CH_3	52.2	33.1	30.0	35.6	42.3	176.6	51.4
C_6H_5[c]	51.3	37.2	30.9	37.3	42.8		
o-$C_6H_4CH_3$[b,d]	52.7	34.6	31.0	35.7	43.9		
$NHCOCH_3$[b]	62.6	33.7	29.9	35.3	41.7	169.8	24.0

[a] Shifts reported in parts per million with respect to internal tetramethylsilane, determined to ±0.05 ppm. [b] Samples run in 5-mm (o.d.) sample tubes. [c] For 1-phenylnorbornane the following additional assignments are tentatively made: C-1′, 146.3; C-2′,6′, 126.2; C-3′,5′, 127.8; and C-4′, 125.4. [d] For 1-*o*-tolynorbornane the following additional assignments are tentatively made: *C*-methyl, 22.7; C-1′, 147.0; C-2′, 135.6; C-3′, 128.5; C-4′, 125.3; C-5′, 124.8; and C-6′, 126.1.

Table II. ^{13}C Substituent Effects of 1-Substituted Norbornanes[a]

X	C-1	C-2,6	C-3,5	C-4	C-7
H	0.0	0.0	0.0	0.0	0.0
Cl	33.5	8.6	1.1	−1.6	8.4
Br	25.8	10.2	1.8	−1.6	9.8
I	1.3	13.2	2.3	−1.8	12.4
OH	46.4	5.6	0.5	−1.6	5.5
OCH_3	51.3	1.2	0.1	−2.5	1.6
OC_2H_5	50.7	1.9	0.2	−2.6	2.3
CH_3	7.3	6.9	1.4	1.4	6.8
CO_2H	15.7	3.1	0.2	1.4	3.9
CO_2CH_3	15.8	3.3	0.2	−0.8	3.9
C_6H_5	14.9	7.4	1.1	0.9	4.4
o-$C_6H_4CH_3$	16.3	4.8	1.2	−0.7	5.5
$NHCOCH_3$	26.2	3.9	0.1	−1.1	3.3

[a] Values refer to differences between the observed chemical shifts of a given compound and that of the unsubstituted hydrocarbon, norbornane. Positive shifts are to lower field (higher frequency) whereas negative shifts are to higher field (lower frequency).

Table III. ^{13}C Chemical Shifts and Substituent Effects of 1-Methoxyadamantane (14)[a]

	C-1	C-2,8,9	C-3,5,7	C-4,6,10
$\delta_C(H)$[b]	28.5	37.9	28.5	37.9
$\delta_C(OCH_3)$[c]	71.2	41.1	30.6	36.6
$\Delta\delta_C$	42.7	3.2	2.1	−1.3

[a] Shifts reported in parts per million with respect to internal tetramethylsilane, determined to ±0.05 ppm. [b] Chemical shifts for adamantane. [c] Chemical shifts for 1-methoxyadamantane; C-methyl 47.7.

variance with those of Lippmaa and Pehk,[4] with the relative shifts varying by 0.4–1.2 ppm. These differences may be due to solvent and/or concentration effects.

To permit more complete comparison with the 1-adamantyl system, 1-methoxyadamantane (14) was also prepared. Analysis of the ^{13}C spectrum as described previously[8,9] afforded the substituent effects given in Table III.

Discussion

The chemical substituent effects summarized in Table II exhibit a wide range of shieldings. In agreement with other reported bridgehead substituted systems, the magnitude of the effect on a given carbon is directly related to the distance it is from the substituent; i.e., α effects > β effects > γ effects > δ effects.[17] This is the expected order for a through-bond effect being transmitted through the bonding network.

As can be seen from Figure 2, the α shieldings at C-1 for the 1-adamantyl and 1-bicyclo[2.2.2]octyl systems correlate reasonably well with each other but do not correlate with those of the 1-norbornanes. This lack of correlation is apparently attributable to the large degree of strain at C-1 of norbornanes. Interestingly, the 1-norbornyl substituent effects correlate more closely with those of the 1-bicyclo[2.2.2]octyl system than those of the 1-adamantyl derivatives, as expected from the relative degrees of strain at C-1 in the three systems. It should also be mentioned that the α-substituent effect of the 1-norbornyl system compares quite favorably to the 4-substituted tricyclenes,[11] a system which is closely analogous to norbornanes at the substituted position.

By contrast the β shieldings at C-2,6 of the 1-norbornyl system correlate reasonably well with those of the 1-adamantanes and 1-bicyclo[2.2.2]octanes (Figure 3). Moreover, as can be seen from Table II, the β shieldings at C-7 correlate well with those at C-2,6; no significant effect is exhibited by the increased strain at C-7, in contrast to the marked effect noted at the α position. The one substituent for which there is no correlation between C-2,6 and C-7 is phenyl, which probably exerts an anisotropy effect at C-2,6.

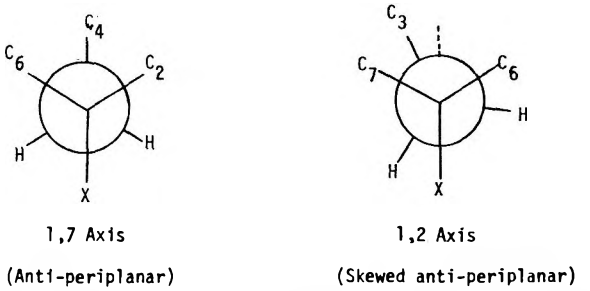


Figure 1. Newman projections along 1,7 and 1,2 axes of 1-substituted norbornyl system.

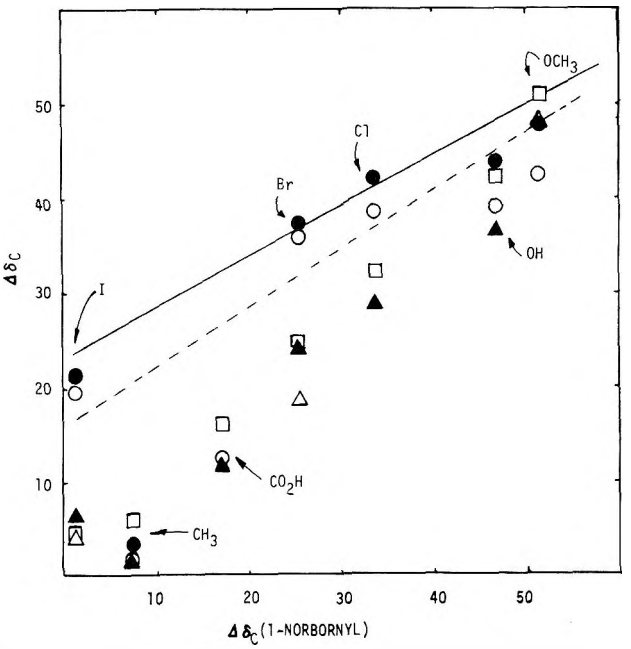


Figure 2. Plot of α-substituent effects of 1-norbornyl system vs. those of 1-bicyclo[2.2.2]octanes (●),[5,7,11] 1-adamantanes (○),[8] 2-adamantanes (▲),[8] 7-norbornanes (△),[5] and cyclohexanes (□).[23]

The interesting longer range substituent effects are seen at C-3,5 and -4. These positions are simultaneously γ and δ to the substituent, depending upon which bridge is considered. The γ arrangements are either antiperiplanar for C-4 or skewed antiperiplanar for C-3,5 (Figure 1), while the δ orientations are gauche-anti for C-3,5 and eclipsed-anti for C-4. The shieldings at C-3,5 correlate reasonably well with γ antiperiplanar shieldings of both of the other bridgehead substituted systems (Figure 4) but they do not correlate as closely as do the β shieldings at C-2,6 and C-7, presumably because the γ arrangements are not truly antiperiplanar.

The observed shieldings at C-4 of the 1-norbornyl systems show no correlation with either the γ or δ substituent effects reported for 1-adamantanes and bicyclo[2.2.2]octanes. However, a reasonable correlation of the C-4 shieldings with the δ effects for the 1-bicyclo[2.2.2]octyl system (Figure 5) is obtained if the C-4 shieldings of norbornane are adjusted by subtracting the γ and δ inductive effects (using the approximation that these are similar at C-3,5 and C-4). On the other hand, when these adjusted C-4 shieldings are plotted against either the γ or δ shielding effects of the 1-adamantyl system, no correlation is found.

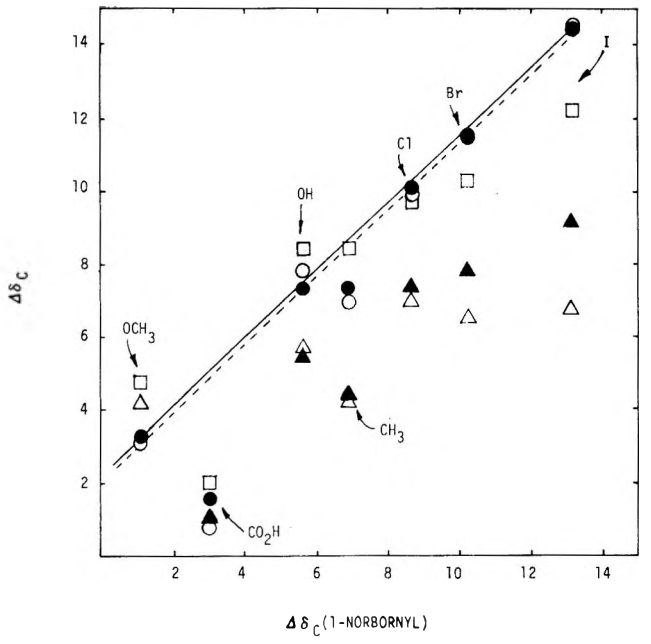


Figure 3. Plot of β-substituent effects at C-2,6 of 1-norbornyl system vs. those for systems given in Figure 2.

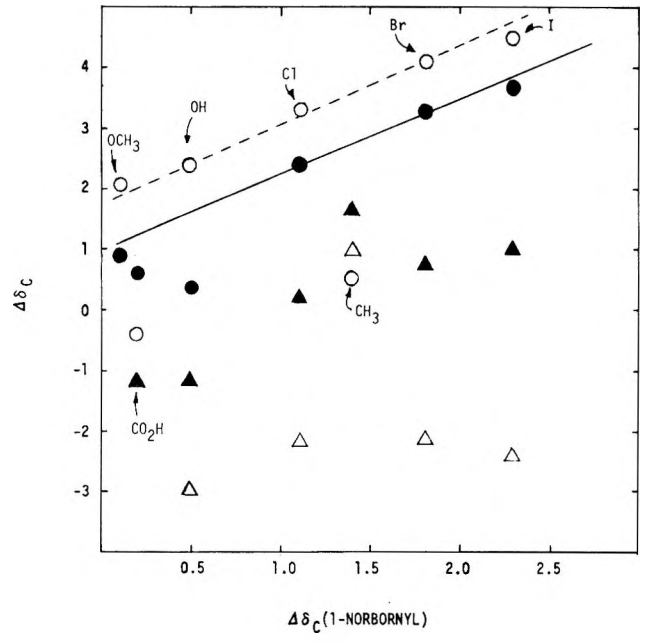


Figure 4. Plot of γ-substituent effects at C-3,5 of 1-norbornyl system vs. those for systems given in Figure 2.

It is obvious that another mechanism in addition to the through-bond effect is influencing the shift at C-4 of both the 1-norbornyl and 1-bicyclo[2.2.2]octyl systems, which have similar C-1–C-4 orientations. Whether this is an electrostatic field effect,[19,20] a through-space α,γ-hyperconjugative effect as proposed by Roberts,[3] or possibly an α,γ-hyperconjugative type interaction as proposed by Eliel et al.,[21] remains unclear. However, field effects are well known in these two systems[22] and probably play at least a contributing role.

As can be seen in Figures 2–5, there was no simple correlation of α-, β-, or γ-substituent effects in 1-norbornyl systems with those previously reported for the 2-adamantyl,[8] 7-norbornyl,[5] or cyclohexyl systems.[23] The one exception to this is the α-substituent effects in cyclohexanes, which correlate surprisingly well with those observed for 1-norbornanes. The origin of this correlation is far from obvious and

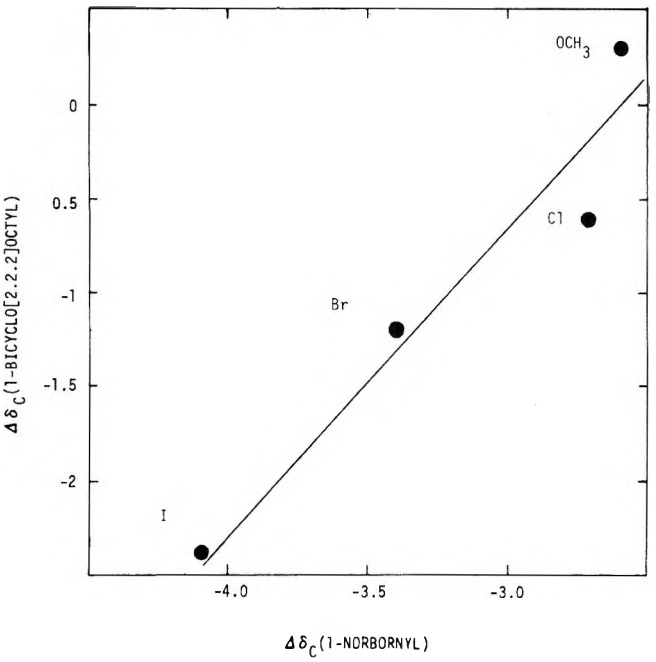


Figure 5. Plot of adjusted substituent effects at C-4 of 1-norbornyl system vs. δ-substituent effects for 1-bicyclo[2.2.2]octanes.

may be fortuitous. Finally, it is noted that the substituent effects in 1-methyladamantane and 1-adamantanecarboxylic acid consistently fail to correlate with the effects observed for other substituents having n electrons on the central atom.

In summary, α-, β-, and γ-substituent effects in the 1-norbornyl system appear to arise principally from through-bond effects. α shieldings are sensitive to strain at C-α but β shieldings are not sensitive to strain at C-β. γ substituent effects at C-3,5 are apparently somewhat influenced by the fact that they do not bear a true antiperiplanar orientation with the substituent at C-1. δ substituent effects at C-4 are not purely inductive; a 1,4 field effect or α,γ-hyperconjugative effect is also involved.

Experimental Section

Measurements. All ^{13}C NMR spectra were obtained at natural ^{13}C abundance with a Varian XL-100 spectrometer operating at 25.2 MHz and employing a VFT-100-SC Fourier transform system with a VDM G20/L computer and interactive disk. FT spectra were obtained using a data length of 16 K and a pulse angle generally <90°. An internal field–frequency lock on deuterium was employed for all pulsed spectra, and pseudorandom proton noise decoupling was used to remove all ^{13}C–H couplings. Unless otherwise indicated, all samples were run in 10-mm o.d. sample tubes and were generally 2–3 M in deuteriochloroform using 3% (v/v) tetramethylsilane as internal reference. Off-resonance decoupled spectra were obtained by setting the proton resonance frequency 500 Hz upfield from Me_4Si.

Materials. All compounds studied, except norbornane, were prepared by standard procedures and their purities in all cases exceeded 98% as determined by gas chromatographic analysis. **Norbornane** (1) was purchased commercially from Aldrich Chemical Co. and used without further purification.

1-Chlorononorbornane (2) was prepared according to the procedure of Bixler and Niemann[24] by treatment of 2,2-dichlorononorbornane with phosphorus trichloride and pentachloride to afford in 61% yield a clear liquid, bp 70° (53 mm), which solidified to a clear waxy solid on standing at room temperature: ν_{max} (CCl_4) 2974, 2932, 2881, 1451, 1310, 1298, 1037, 992, 947, 905, and 838 cm^{-1}; ^1H NMR (CCl_4) δ 2.18 (br s, 1, CH-4) [lit.[24] bp 70–71 °C (54 mm)].

1-Bromonorbornane (3) was prepared by a modification of the Cristol–Firth Hunsdiecker reaction[25] by treatment of 1-norbornanecarboxylic acid[24,26] with red mercuric oxide and bromine in bromotrichloromethane to afford in 44% yield a clear liquid: bp 62–64 °C (23 mm); ν_{max} (neat) 2968, 2926, 2877, 1451, 1309, 1296,

1253, 1227, 978, 947, 897, 832, and 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m) [lit.[27] bp 56° (18 mm)].

1-Iodonorbornane (4) was prepared according to the procedure of Lansbury et al.[28] by treatment of 1-chloronorbornane with lithium metal and iodine to afford in 44% yield a colorless liquid, bp 80–82 °C (12 mm), which solidified when placed into a freezer: ν_{max} (CCl_4) 2960, 2875, 1451, 1309, 1295, 1253, 1228, 972, 932, 892, and 838 cm^{-1}; ^1H NMR (CCl_4) δ 1.88 (br s, 9) and 1.37 (br m, 2) [lit.[28] bp 75° (10 mm)].

1-Norbornanol (5) was prepared by the general photochemical procedure of Kropp et al.[29,30] Irradiation of 1-iodonorbornane in aqueous solvents afforded approximately 60% of the alcohol as a colorless, waxy solid: mp 151–153 °C (sealed capillary); ν_{max} (CCl_4) 3617, 3330, 2961, 2922, 2874, 1451, 1315, 1210, 1135, 1089, and 919 cm^{-1}; ^1H NMR (CCl_4) δ 3.50 (s, 1, OH), and 2.05 (br s, 1, CH-4) [lit.[31] mp 152–154 °C (sealed capillary)].

1-Methoxynorbornane (6) was also prepared by the same photochemical procedure.[29,30] Irradiation of iodide 4 in absolute methanol yielded approximately 90% of the methyl ether as a colorless liquid: ν_{max} (CCl_4) 2959, 2875, 2838, 1450, 1362, 1318, 1219, 1190, 1139, 1092, and 1035 cm^{-1}; ^1H NMR (CCl_4) δ 3.20 (s, 3, OCH_3), and 2.06 (br s, 1, CH-4); *m/e* 126.1044 (calcd for $C_8H_{14}O$, 126.1045) and 97 (100).

1-Ethoxynorbornane (7) was prepared by the similar irradiation[29,30] of iodide 4 in anhydrous ether or absolute ethanol to give the desired ether in approximately 60–70% yield as a colorless liquid: ν_{max} (CCl_4) 2950, 2935, 2873, 1450, 1317, 1262, 1222, 1170, 1139, 1100, 1046, 937, and 895 cm^{-1}; ^1H NMR δ 3.44 (q, J = 7.5 Hz, 2, CH_2CH_3), 2.05 (br s, 1, CH-4), and 1.13 (t, J = 7.5 Hz, 3, CH_2CH_3); *m/e* 140.1201 (calcd for $C_9H_{16}O$, 140.1199), 111 (73), 83 (100), and 55 (28) [lit.[32] ν_{max} (CCl_4) 1140 cm^{-1}; ^1H NMR (CCl_4) δ 4.38 (q, J = 7 Hz, 2), 2.0 (s, 1), and 1.1 (t, J = 7 Hz, 3)].

1-Methylnorbornane (8) was prepared by the catalytic hydrogenation of 1-methylnorbornene in methanol[33] to produce the hydrocarbon 8 as a colorless liquid: ν_{max} (CCl_4) 2999, 2869, 1450, 1376, 1330, 1304, and 1212 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (br s, 1, CH-4) and 1.14 (s, 3, OCH_3).

1-Norbornanecarboxylic acid (9) was prepared by basic hydrolysis of the methyl ester **10**[34] to afford the acid in 91% yield as an odoriferous, white solid: mp 109–110°; ν_{max} (CCl_4) 3390–2450, 1699, 1425, 1309, 1254, 1226, 940, 814, and 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.9 (s, 1, CO_2H) and 2.39 (br s, 1, CH-4) (lit.[24] mp 113.8–115.5°).

1-Norbornanecarboxylic acid methyl ester (10) was prepared by treatment of 2-*exo*-bromonorbornane-2-*endo*-carboxylic acid methyl ester[26,34] with zinc and acetic acid to afford the ester in 81% yield: bp 66–67 °C (9 mm); ν_{max} (neat) 2958, 2927, 2875, 1730, 1435, 1336, 1242, 1219, 1109, 1073, and 759 cm^{-1}; ^1H NMR (CCl_4) δ 3.63 (s, 3, OCH_3) and 2.31 (br, 1, CH-4) [lit.[34] bp 52–53 °C (1.8 mm)].

1-Phenylnorbornane (11) was prepared as a clear liquid in greater than 85% yield by the general irradiation procedure of 4 in benzene:[29,30] ν_{max} (CCl_4) 3087, 3068, 3011, 2949, 2921, 2871, 1605, 1495, 1450, 1335, 1077, 1036, and 700 cm^{-1}; ^1H NMR (CCl_4) δ 7.15 (m, 5, aromatic H), and 2.32 (br s, 1, CH-4) [lit.[35] ^1H NMR δ 7.15 (5) and 2.32 (1)].

1-*o*-Tolynorbornane (12) was prepared and separated from its isomers in approximately 50% overall yield as a clear oil by the irradiation of 4 in toluene:[29,30] ν_{max} (neat) 3097, 3055, 2949, 2869, 1597, 1481, 1446, 1371, 1319, 1229, 1238, 1112, 1050, and 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (m, 1, aromatic H), 7.24 (d, J = 3.5 Hz, 3, aromatic H), 2.51 (s, 3, *o*-CH_3), and 2.34 (br s, 1, CH-4); *m/e* 186.1405 (calcd for $C_{14}H_{18}$, 186.1408), 186 (38), and 147 (100).

***N*-(1-Norbornyl)acetamide (13)** was isolated in approximately 45% yield as a colorless, crystalline solid, mp 161–162 °C (sealed capillary), from the irradiation of 4 in aqueous acetonitrile:[29,30] ν_{max} ($CHCl_3$) 3448, 3340, 2960, 2939, 2878, 1666, 1508, 1370, 1340, 1310, and 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (br m, 1, NH), and 1.95 (s, 4, CH_3 and CH-4); *m/e* 153.1158 (calcd for $C_9H_{15}NO$, 153.1154), 124 (73), and 82 (100).

1-Methoxyadamantane (14) was prepared in approximately 90% yield as a clear liquid by treatment of 1-iodoadamantane[36] with an excess amount of silver perchlorate in methanol solution at room temperature: bp 60–61 °C (1.2 mm); ν_{max} (CCl_4) 2908, 2856, 2828, 1447, 1351, 1306, 1199, 1176, 1111, 1087, 1048, 890, and 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, 3, OCH_3) and 2.20 (s, 3, bridgehead H) [lit.[37] bp 66–68 °C (3 mm); ν_{max} (CCl_4) 2907, 2849, 1445, 1350, 1302, 1111, 1086, 1050, and 890.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (s, 3, OCH_3)].

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Registry No.—**2**, 765-67-3; **3**, 13474-70-9; **4**, 930-80-3; **5**, 51566-98-4; **6**, 57901-28-7; **7**, 33357-81-2; **8**, 10052-18-3; **9**, 18720-30-4; **10**, 2287-57-2; **11**, 24892-79-3; **12**, 57901-29-8; **13**, 57901-30-1; **14**, 6221-74-5.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Polycyclic δ-Lactones

Miroslav J. Gašić* and Zoltan Djarmati

Department of Chemistry, Faculty of Science, University of Belgrade, Belgrade, Yugoslavia 11001

S. William Pelletier*

Natural Products Laboratory, Department of Chemistry, University of Georgia, Athens, Georgia 30602

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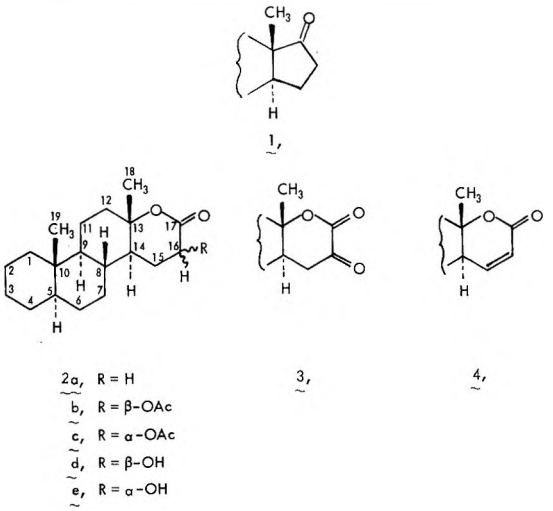
The ^{13}C NMR spectra of the steroidal and terpenoid δ-lactones, deoxyandrololactone and its C-16 epimeric acetoxy and hydroxy derivatives, and ambreinolide and its C-12 epimeric acetoxy derivatives, as well as their corresponding α,β-unsaturated derivatives, have been obtained by the Fourier transform technique at 25.03 MHz. The spectra are analyzed in terms of earlier investigations in the steroid and terpene series, using empirical correlations and single frequency off-resonance decoupling experiments. On the basis of chemical shift data, two conformations, the half-chair and twisted boat, may be proposed for the cited β- and α-oriented α-oxy-substituted δ-lactones, respectively.

Polycyclic natural products frequently contain a δ-lactone ring whose structural features sometimes remain insufficiently clarified. Although ^{13}C NMR spectroscopy is a powerful method for structural analysis, no systematic study of lactones by this method has yet been reported; however, the recent work by Carrol et al.[1] on the configuration and conformation of 3,5-dimethyl valerolactones has provided valuable spectral data for simple versions of such systems. Our earlier interest in δ-lactones[2,3] resulted in the preparation of a number of structurally related compounds which provided an opportunity to obtain basic information on factors affecting the chemical shift of carbons in lactones of more complex and rigid structure.

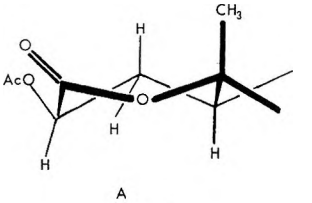
The assignment of individual resonances in compounds **1–4** (Table I) was made on the basis of earlier investigations in the steroid series,[4] empirical correlations, and single frequency off-resonance decoupling experiments.[5] As expected, the modification of ring D to a six-membered lactone ring does not alter the chemical shift of remote carbons (C-1 to C-6, C-10, C-11) relative to those in the parent steroid 5α-androstane derivative (**1**). The remaining carbons outside the lactone ring (C-7, C-8, C-9, and C-12) suffer minor changes of position of their respective resonances. As a consequence of ring D enlargement, C-7 is shifted upfield (1.1 ppm), probably from introduction of a new γ-H···H interaction[6] with the hydrogen at C-15. The same modification of ring D produces a decrease of steric interaction between the angular C-18 methyl group and axial hydrogen at C-8 and, therefore, must be partly responsible for the downfield shift of its resonance. Finally, the upfield shift of the highly hindered C-9 could not be attributed to any specific interaction but rather reflects a minor overall change in environment.



The assignment of lactone ring carbons (C-13 to C-17) was easily achieved by empirical correlations throughout the series and by sford techniques; the recorded resonances are within the limits predicted by the chemical shift theory. The relatively high upfield position of both the C-17 carbonyl carbon and the C-16 α-methylene carbon in **2a** (C-13 and C-12 in **5a**, respectively) confirm the assumption that factors affecting the chemical shift of lactone ring carbons differ substantially from those determining the shielding of carbons in the corresponding cycloanones.[7]

The chemical shifts of carbons 14, 15, and 16 in the acetoxylated steroidal ring D lactones are interesting and may have some bearing on the conformation of the δ-lactone ring. First, it can be observed that the carbinyl carbon shieldings (C-16) in **2b** and **2c** reflect the configurational difference, as expected for different contributions of quasi-equatorial and quasi-axial acetoxy groups, respectively (Δδ 3.0 ppm).[9] The striking feature of the data is the magnitude of downfield shifts of neighboring C-15 carbons, which are not concomitant with recognized β effects of such isomeric acetoxy groups in chairlike conformations,[4a,10] the deshielding difference found being in favor of the quasi-axial epimer (Δδ 2.3 ppm). These seemingly contradictory findings, particularly in view of the absence of any γ effect at C-14 in either of the acetoxy epimers, can be accommodated by assuming different conformations for the two lactones **2b** and **2c**. Based on the earlier proposed coplanarity of the ethereal oxygen, the carbonyl group, and the two adjacent carbons,[8] two conformations may be proposed for lactones **2b** and **2c**, the half-chair A and the twisted boat B, respectively.

The proposed conformations A and B explain why introduction of an acetoxy group at C-16 does not result in a significant shielding γ effect at C-14 in either of the epimers **2b** or **2c**, relative to the unsubstituted lactone **2a**. Further-



A

2b, and 5b

Table I. Carbon-13 Chemical Shifts and Assignments for Steroidal δ-Lactones[a]

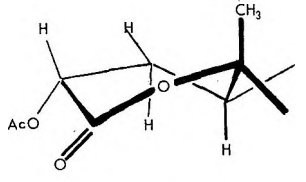
Carbon	1	2a	2b	2c	2d	2e	3	4
1	38.7	38.4	38.4	38.5	38.4	38.3	38.5*	38.4
2	22.1†	22.0	22.0	21.9	21.9	21.9	21.9	22.0
3	26.8	26.6	26.7‡	26.6	26.6	26.5	26.5	26.6
4	29.0*	28.7	28.7†	28.5	28.5*	28.6	28.4†	28.7*
5	47.0	46.4	46.3*	46.3	46.3	46.3	46.3	46.7
6	28.8*	28.7	28.5†	28.5	28.5*	28.6	28.6†	28.5*
7	31.7	30.6	30.6	30.5	30.7	30.7	30.2	30.4
8	35.1	37.9	37.2	38.5	37.1	38.6	38.5	35.2
9	54.9	53.5	53.4	53.2	53.5	53.0	52.8	54.2
10	36.4	36.2	36.2	36.2	36.2	36.1	36.2	36.4
11	21.8†	21.6	21.6	21.6	21.6	21.6	21.6	21.5
12	31.0	39.4	38.9	39.5	38.8	39.4	38.8*	38.4
13	47.7	83.1	85.4	84.4	86.3	85.1	84.7	83.3
14	51.6	46.4	46.7*	46.3	46.3	46.3	45.8	48.6
15	20.1	19.8	26.8‡	29.1	28.2*	30.5	38.1	145.4
16	35.8	28.7	68.6	65.6	68.3	64.5	190.3	121.6
17	220.7	170.9	168.5	168.3	174.8	174.8	157.4	163.7
18	13.8	20.1	20.7	19.5	21.1	19.3	20.6	18.5
19	12.2	12.0	12.0	12.0	12.1	12.0	12.0	12.0

[a] In parts per million downfield relative to Me_4Si. Solvent deuteriochloroform. The two carbon resonances at the acyl groups of **2b** and **2c** occur at 169.5 and 20.7 ppm. *,†,‡ Values within any vertical column may be interchanged.

Table II. Carbon-13 Chemical Shifts and Assignments for Terpenoid δ-Lactones[a]

Carbon	5a	5b	5c	6
1	39.2	39.3	38.8	38.6
2	18.4	18.4	18.2	18.1
3	41.8	41.8	41.7*	41.8
4	33.2	33.3	33.1	33.1
5	56.0	56.0	55.8	56.1
6	19.7	19.8	19.6	19.7
7	41.3	40.8	41.4*	39.8
8	83.5	85.8	84.9	84.0
9	53.7	53.5	53.1	55.4
10	37.2	37.4	37.3	36.5
11	15.8	24.0	24.6	145.4
12	29.0	69.1	65.5	122.2
13	171.2	168.5	168.4	163.9
17	22.9	23.5	22.7	21.0
18	33.3	33.3	33.3	33.1
19	21.5	21.3	21.5	21.4
20	15.1	15.7	14.4	17.0

[a] In parts per million downfield relative to Me_4Si. Solvent deuteriochloroform. The two carbon resonances of the acyl groups of **5b** and **5c** occur at 169.6 and 20.7 ppm. * Values within any vertical column may be interchanged.



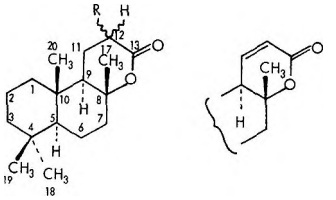
B

2c, and 5c

more, the twisted boat conformation B allows a substantial decrease in the C-18 methyl group eclipsing effect[11] at C-15, thus accounting for its greater relative deshielding in epimer **2c**. Finally, the greater shielding of the C-16 carbinyl carbon in lactone **2c** may be attributed to the eclipsing effect of the C-18 methyl group, i.e., to a greater steric congestion in the twisted boat form B. It should be noted that a similar conformational relationship for pairs of epimeric steroidal α-acetoxy ketones was proposed earlier by Johnson et al. on the basis of their proton NMR spectral data.[12]

The chemical shift of carbons in hydroxy lactones **2d** and **2e** follows the same general pattern, complementing both the assignments and the above arguments, the same being true for the remaining compounds **3** and **4** of the steroid series. However, the substituent-dependent variation of the C-17 lactone carbonyl carbon shielding over a range of ~17 ppm (Table I) should be noted. Although the interpretation of the apparent trend based solely on the electron-releasing properties of neighboring substituents is oversimplified, it seems still useful for a qualitative assessment of the degree of the carbonyl π-bond polarization toward oxygen.

The analysis of the terpene series (compounds **5–6**, Table II) was made on the basis of similar methods and also by correlation with relevant model systems such as the pimaradienes,[13] 9-methyldecalins, and perhydrophenanthrenes.[14] The results are in good agreement with those of



5a, R = H
b, R = β-OAc
c, R = α-OAc

6

the steroidal lactones. Again, introduction of an acetoxy group into the lactone ring (epimers **5b** and **5c**) does not lead to an upfield shift of the carbon in the γ position (C-9), indicating the same substituent-dependent conformational selectivity in α-acetoxylated δ-lactones, i.e., conformations A and B for lactones **5b** and **5c**, respectively. The conformational difference, however, between epimers **5b** and **5c** results in a reduced impact on the deshielding of C-11 in the latter when compared with the chemical shift difference of the corresponding C-15 carbon in the epimeric steroidal lactones **2b** and **2c**. The reduced deshielding of the C-11 carbon[11] neighboring the carbinyl carbon in **5c** is probably a result of the increased eclipsing effect of the C-20 methyl group. Thus, decreasing the C-17 methyl group eclipsing effect at C-11 through the twisted conformation B of **5c** is being partially replaced by this new inter-

action, the assumption being supported by an upfield shift of C-20 in **5c** by 1.3 ppm.

This initial effort in ^{13}C NMR analysis of complex lactone systems has supplied some rather interesting data; more basic information, particularly that pertaining to electric field effects in α-oxygenated carbonyl compounds, is needed before any generalizations can be drawn.

Experimental Section

Carbon-13 spectra were determined at 25.03 MHz in the Fourier mode using a JEOL-PFT-100 spectrometer in conjunction with an EC-100 20K memory computer. The spectrometer features a deuterium lock system, a JNM-SD-HC random noise (2500-Hz bandwidth) proton decoupler, and JNM-DP-1 digital pulse programmer. Spectra of the compounds were determined in ~0.5 M deuteriochloroform solution (which also provided the lock signal) with 5% Me_4Si added as internal reference. All samples were contained in precision ground 10 mm o.d. tubes. The spectrometer was used in the crosscoil configuration. On the average, a 12-μs pulse, corresponding to an approximate tilt angle of 45°, was employed. For the average spectral width of 5000 Hz the delay between pulses was 3 s.

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Registry No.—**1**, 963-74-6; **2a**, 2466-25-3; **2b**, 42516-17-6; **2c**, 42516-18-7; **2d**, 42516-15-4; **2e**, 42516-16-5; **3**, 42516-19-8; **4**, 57901-22-1; **5a**, 468-84-8; **5b**, 54632-03-0; **5c**, 54656-75-6; **6**, 52811-58-2.

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Synthesis and Characterization of Some Polycyclic Cyclobutanones

R. D. Miller,* D. L. Dolce, and V. Y. Merritt

IBM Research Laboratory, San Jose, California 95193

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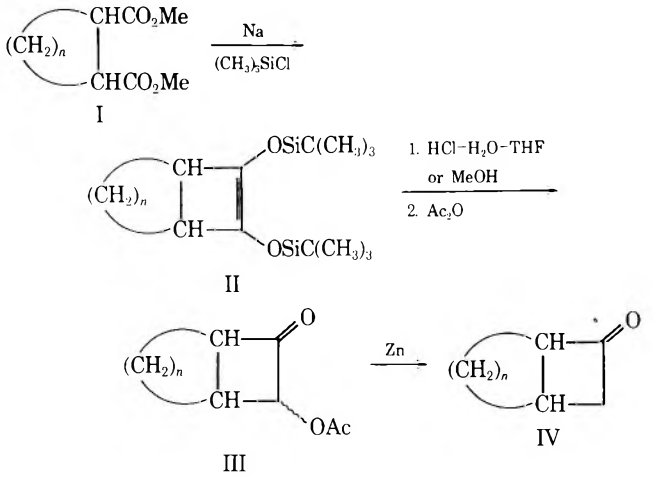
A new stereospecific synthesis of 2,3-cis fused polycyclic cyclobutanone derivatives from readily available starting materials is described. The technique provides a valuable compliment to the use of dichloroketene in that it can be run on a large scale, makes efficient use of reagents, and in a number of cases (e.g., **16** and **22**) gives much higher yields of the ketone than the former technique. In addition, the complimentary endo isomers **18**, **20**, **24**, and **26** are formed in cases where dichloroketene has been demonstrated or predicted to occur stereospecifically to produce the exo isomers. The ultraviolet spectra of the ketones have been examined for evidence of nonconjugated chromophore interaction. The exo unsaturated derivative **22** shows a strong intensification of the $n \rightarrow \pi^*$ transition most reasonably described in terms of a geometric dependent interaction between the π orbitals of the double bond and those of the carbonyl group via the exo σ bond α to the carbonyl group.

The synthesis of fused ring and polycyclic cyclobutanones in preparatively useful yields has been a difficult problem. The most commonly used techniques have involved the thermal cycloaddition of ketene and alkyl and aryl substituted derivatives to olefins and dienes to yield cyclobutanones directly.[1] This technique has suffered from a lack of generality, and difficulty in large-scale preparations. The latter has been particularly obvious in cycloadditions involving ketene itself. The discovery that the highly reactive intermediate, dichloroketene, could be generated in situ and trapped by olefins and dienes has surmounted some of these difficulties.[2] This novel reagent allows the preparation of many cyclobutanone derivatives in good yield and exhibits high regio- and stereospecificity. Still some difficulties remain even with this reagent. For example, certain olefins and dienes give rather low yields of cycloaddition products[3] and with unreactive reagents, a relatively large excess of the ketenophile is generally necessary to produce useful quantities of product. Ironically, even the regio- and stereospecificity of the reagent can be a disadvantage if the isomeric derivative is the one desired. We have sought a reaction sequence which (1) makes efficient use of scarce reagents, (2) produces cyclobutanones in good yields where the dichloroketene method does not, and (3) is stereospecific but in a complimentary sense to dichloroketene. This paper describes a technique for the large-scale, stereospecific, and high-yield preparation of a number of fused ring and polycyclic cyclobutanones from readily available starting materials. The overall synthetic sequence is described in Scheme I.

Results and Discussion

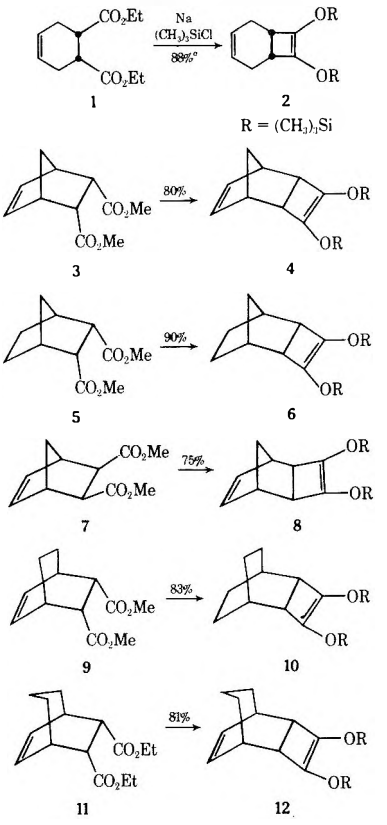
The first step in the sequence involves the acyloin condensation of the corresponding diesters using the basic technique described by Bloomfield.[4] All of the acyloin condensations went smoothly and in good yield in spite of a potential complicating factor of having a strained double bond in close proximity to the reactive centers in **3**, **9**, and

Scheme I



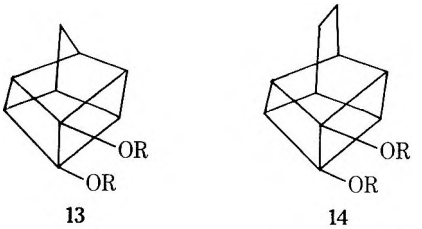
11 (see Table I). The bistrimethylsiloxy derivatives are all fluid, high-boiling liquids, colorless when pure, which are thermally stable but hydrolytically labile. Their infrared spectra are characterized by a vinyl ether band at ca. 1710 cm^{-1} and additional strong bands between 830–1000 and 1250–1430 cm^{-1}. The mass spectra of these compounds showed strong parent peaks and an intense fragment at *m/e* 73 [loss of $(CH_3)_3Si$]. The symmetry of the disiloxene derivatives is apparent from their NMR spectral data. For example, the NMR spectrum of **2** (see Table I) shows only four resonances at τ 4.40 (m, 2 H), vinyls, 7.40 (m, 2 H), cyclobutylmethines, 7.96 (m, 4 H), allylic, and 9.83 (s, 18 H), trimethylsiloxy protons. Since the ultimate usefulness of the synthesis depended on the retention of the ester geometry upon condensation, the stereochemistry of the bis(trimethylsiloxy)cyclobutene derivatives was further investigated. Molecular symmetry and geometric flexibility allowed no facile assignment of the relative stereochemical relationship of the cyclobutene methine protons in **2** by NMR. However, it seems extremely unlikely that the ring juncture is trans fused, since Bloomfield has shown that this is unstable with respect to the ring-opened product under the reaction conditions.[4] Consistently, when a neat sample of **2** was heated in a sealed tube to 190 °C for 12 h no significant isomerization could be detected by ir, NMR, or GLC. It was similarly anticipated that the stereochemistry of the bicyclic esters would be maintained under the cyclization conditions and this was confirmed by spectral and chemical means. The spectrum of **4** (see Table I) shows five main absorptions at τ 4.2 (t, J = 1.5 Hz, 2 H), 7.38 (d, J = 3 Hz broadened by additional splitting, 2 H), 7.51 (complex m, 2 H), 8.37 (AB q, J = 8.5 Hz, 2 H), and 9.90 (s, 18 H). The separation between central peaks of the AB quartet was δ 0.29. The considerable chemical nonequivalence of the bridge methylene protons is most consistent with the endo geometry.[5] Furthermore, double resonance experiments showed that the vinyl protons were coupled to the multiplet at τ 7.51 but not to the broad two-proton doublet at τ 7.38. From the models, the dihedral angle between the cyclobutane methine and the bridgehead protons in the endo derivative is ca. 40–45°. Simple extrapolation from a Karplus plot[6] predicts a coupling constant of 2.8–4.5 Hz, which is consistent with the observed valve of 3 Hz. Direct chemical evidence of the endo geometry was obtained by photolysis of **4**. Irradiation of **4** (0.15 M, 254 nm) in cyclohexane or ether produced 4,5-bis(trimethylsiloxy)homocubane (**13**) in almost quantitative yield.[7] The geometry of the saturated derivative **6** was verified as endo by its NMR spectrum, which again showed the cyclobutene methine

Table I



a Yields of purified material.

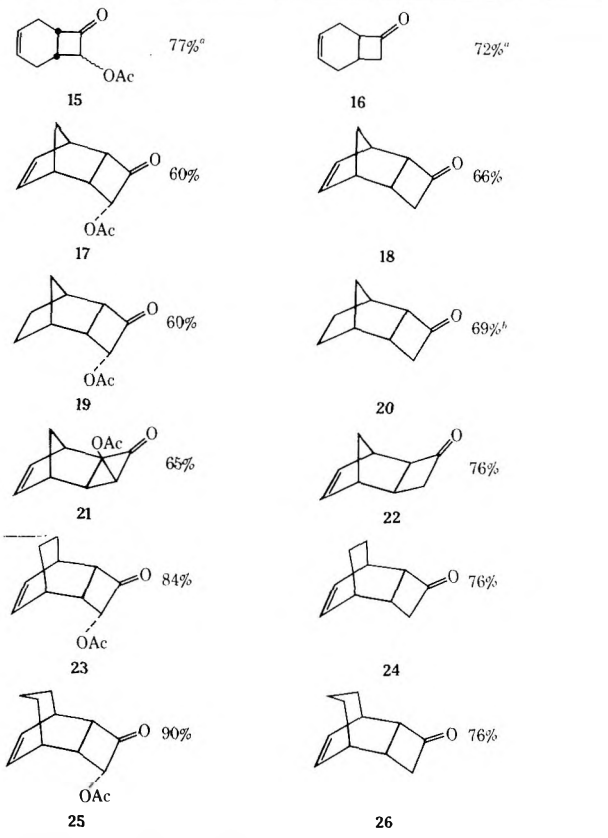
protons as a broad doublet (J = 3 Hz) complicated by further small splittings. The assignment of the exo geometry to derivative **8** followed logically again from consideration of its spectral data. The NMR spectrum of **8** shows the following absorptions: ($CDCl_3$) τ 3.90 (t, J = 2 Hz, 2 H), 7.51 (m, 2 H) bridgehead, 7.82 (s, $W_{1/2}$ = 2 Hz, 2 H), cyclobutene methines, and 8.48 (AB q, J = 9 Hz, 2 H). The upfield shift of the cyclobutene methine protons by ca. δ 0.44 relative to **4** is consistent with the expected increased shielding by the double bond of the norbornene moiety. Consistently, they appear as a slightly broadened singlet due to the small bridgehead coupling constant.[5] The separation between the central peaks of the AB quartet is only δ 0.18 compared to δ 0.29 in **4** reflecting the increasing similarity of chemical environment of the bridge methylene protons caused by the presence of the additional double bond in the exo position. Although NMR could not be conclusively used to confirm the stereochemistry of **10** as endo, it was again found that irradiation of a 0.15 M solution of **10** in cyclohexane produced the cage product **14** in ca. 6% yield.[7] The endo geom-



etry of compound **12** was assumed by analogy, since analysis of the NMR spectrum was inconclusive and **12** failed to undergo photochemical cycloaddition under the conditions described above.

It has been reported[4,8] that disiloxene derivatives can be hydrolyzed to the corresponding acyloins in neutral solu-

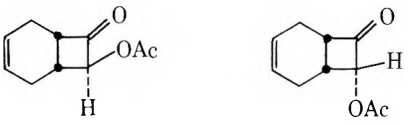
Table II



[a] Yields of purified material. [b] Based on reacted starting material.

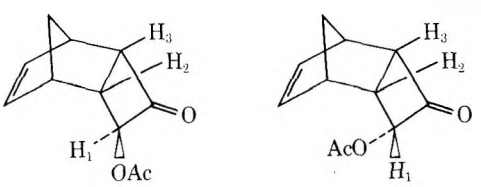
tion by refluxing methanol or by the use of dilute hydrochloric acid in tetrahydrofuran. During the course of our work, we have investigated both techniques. The alcoholysis reaction usually generated the acyloin in good yield and was experimentally a more convenient overall procedure. However, it was observed that occasionally, for no obvious reason, a mixture of ketals would be formed instead of or in addition to the desired acyloin. This occurred even though the glassware had been previously base treated and the methanol distilled from sodium methoxide. While this anomalous alcoholysis occurred rather infrequently, its unpredictability led us to favor the use of aqueous acid which produced the acyloins in yields comparable to the alcoholysis technique.[9] Owing to the potential instability of the acyloins, they were not further purified, but converted directly to the corresponding keto acetates with acetic anhydride. This was accomplished using refluxing acetic anhydride (2–3 h) or acetic anhydride–pyridine at room temperature (12–15 h). In those systems where the procedures were compared, the yields were similar and the acetic anhydride–pyridine method was favored owing to the simplified work-up procedure. The results of hydrolysis and acetylation are shown in Table II. All of the keto acetates were characterized by strong ir bands at 1780 (cyclobutanone), 1745 (acetate carbonyl), and 1230 cm^{-1} (acetate carbon–oxygen stretching).

While the hydrolysis and acetylation sequence might be expected to generate a epimeric mixture of keto acetates depending on the mechanism and steric environment, this was positively demonstrated in only one case. The hydrolysis of **2** using either methanol or aqueous acid and subsequent acetylation produced a mixture of two keto acetates, **15a** and **15b**, in approximately 1/4 ratio. The crude mixture could be converted directly to the ketone **16** in good yield upon subsequent treatment with zinc dust and acetic acid. The major isomer was collected with difficulty by GLC and had the following NMR spectrum: τ (CCl_4) 4.22–4 45 (m, 3 H), 6.57–7.36 (complex multiplet, 2 H), and 7.48–8.06 (multiplet containing superimposed acetate singlet, 7 H). The minor isomer, which was enriched during collection, showed very similar spectral data to the major with the most significant differences in its NMR spectrum. In the vinyl region a two-proton multiplet appeared at τ 4.03 and the cyclobutyl methine proton α to the acetate group appeared upfield as a doublet of doublets (J = 7, 3 Hz) at τ 5.05. The acetate resonance of the minor isomer was at only slightly higher field than the major isomer (7.99 vs. 7.96). Although conformational mobility of the basic carbon skeleton makes assignment of the geometry of the acetate group difficult, it seems reasonable that the upfield shift of the acetate methine proton in the minor isomer relative to the major ($\Delta\delta$ 0.70) is a result of increased shielding by the internal double bond. This led to a tentative assignment of geometry **15a** to the minor and **15b** to the major isomer.



15a **15b**

This assignment is also attractive from a mechanistic point of view, since the formation of predominantly **15b** can be rationalized on the basis of kinetic protonation from the least hindered side during hydrolysis. The other keto acetates **17**, **19**, **21**, **23**, and **25** (see Table II) were formed predominantly as one stereoisomer as determined by NMR and GLC analysis. Assuming again protonation from the least hindered side, one would predict in each case that the acetate group should appear trans to the cyclobutane ring juncture protons. Since the tricyclic systems are considerably more rigid, assignment of the acetate configuration by the magnitude of the coupling constants can be made with more confidence.[10] This assignment is facilitated by the fact that in each of the tricyclic cases the tertiary proton α to the acetate group appears downfield as a doublet of doublets in the region τ 4.3–4.7. For the keto acetate **17**, which represents the most rigid of the materials prepared, models indicate that the cyclobutanone ring is nearly planar. The acetate methine proton of **17** appears at τ 4.68 as a doublet of doublets (J = 8.5, 3.5 Hz). Since the larger coupling is most probably due to the vicinal protons H_1 and H_2 rather than the long-range $H_{1,3}$ interaction,[10c] a stereochemical assignment is made based on the respective dihedral angles. The dihedral angle between H_1 and H_2 in **17b** is ca. 0°, while in **17a** it is ca. 117°. On this basis, consideration of



17a **17b**

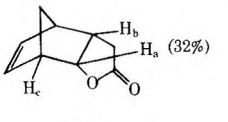
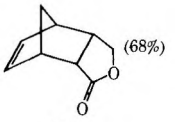
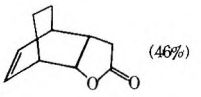
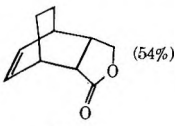
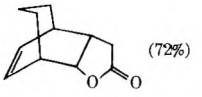
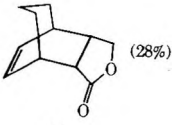
the relatively large vicinal coupling constant (J = 8.5 Hz) of the product leads to the most probable structural assignment of **17b** as the keto acetate formed upon hydrolysis and subsequent acetylation of **4**. Similarly in each of the additional keto acetates **19**, **21**, **23**, and **25** the acetate methine proton appeared as a doublet of doublets ($J_{1,2}$ = 8.5–9.0, $J_{1,3}$ = 3.0–4.0 Hz) and was tentatively assigned the same stereochemistry. It is interesting to note that the steric interaction of the methylene bridge protons in **21** is still

apparently great enough to dictate the formation of predominantly one acetate.

The subsequent reductive elimination from the keto acetates was accomplished without complications using zinc in refluxing acetic acid (see Table II). Under these conditions the production of **20** was quite slow, and even after heating for 39 h, 30% of the starting material remained. The slow rate of elimination may arise from steric hindrance to the loss of acetate caused by the presence of the endo hydrogens. The ketones were produced as colorless volatile liquids (**16, 22, 26**) or as waxy semisolids (**18, 20, 24**). All materials were characterized by analytical and spectral data supported by unambiguous synthesis or chemical transformation where necessary. Each of the ketones showed a strong band between 1775 and 1780 cm^{-1} (cyclobutanone) in the infrared and an intense parent ion in their mass spectra (70 eV). The NMR spectra, which are generally quite complex, are reported in detail in the Experimental Section and for this reason only a few pertinent points will be discussed here. For all of the endo tricyclic ketones (**18, 20, 24,** and **26**) a complex single-proton resonance appears downfield from the rest of the absorptions. This low-field signal is most reasonably assigned to the exo methine proton α to the carbonyl group. In the case of **22** and its saturated derivative **33,** this proton is upfield and merged with other resonances. Another feature which bears on the geometry of the cyclobutanone moiety in **18** and **22** is the separation between the two central peaks of the AB quartet due to the bridge methylene protons. As previously observed for **4** and **8,** the separation in **18** is δ 0.24, while in **22,** where the protons are more nearly equivalent owing to the additional shielding effect of the carbonyl group, it is only δ 0.18.

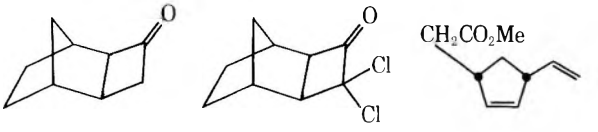
The NMR spectra of the cyclobutanones were rather complex, and chemical methods were used to further verify structures and stereochemistry. Since the photochemical cycloelimination of ketene from simple 2,3-disubstituted cyclobutanones shows high steroselectivity often described in terms of the most stable acyl-alkyl biradical,[11] this was used to confirm the structure of **16.** Accordingly, irradiation of **16** in pentane produced 1,4-cyclohexadiene and 3-norcarene in 58 and 13% yields, respectively. Additional confirmation was obtained by hydrogenation of **16** (hexane, PtO_2) with 1 equiv of hydrogen to produce bicyclo[4.2.0]octan-7-one, whose spectral properties were identical with those reported by Blomquist and co-workers.[12] The structure and stereochemistry of the endo ketones **18, 24,** and **26** were probed via Baeyer–Villiger oxidation (see Table III). Treatment of **18** with basic hydrogen peroxide generated the corresponding lactones **27** and **28** (60%).[13] The lactone **28** was synthesized in an unambiguous manner by reduction of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride at −60 °C with lithium aluminum hydride using the method described by Bloomfield and Lee.[14] The endo geometry of **27** was assured by NMR analysis. The methine proton H_a (see Table III) appeared downfield at τ 5.06 as a doublet of doublets (J = 7, 4 Hz) due to splitting by H_b and H_c. The relatively large coupling with the bridgehead proton H_c (J_{ac} = 4 Hz) is indicative of an exo position for this proton.[5] Since the Baeyer–Villiger reaction is known to proceed with retention of configuration of the migrating group,[15] this assures the expected endo geometry for the ketone **18.** Similar applicaton of the oxidation procedure to **24** and **26** produced the results shown in Table III. Catalytic hydrogenation of **18** (PtO_2, hexane) produced the saturated derivative **20** identical in every way with the sample produced from the application of the described reaction sequence to the saturated endo ester **5.** The exo ketone, **22,** could be similarly hydrogenated to the saturated derivative

Table III. Results of Baeyer–Villiger Oxidation

Ketone	Lactones	
	[60%][a]	
18	 (32%)	 (68%)
	27	**28**
	[76%]	
24	 (46%)	 (54%)
	29	**30**
	[85%]	
26	 (72%)	 (28%)
	31	**32**

[a] Total lactone yield.

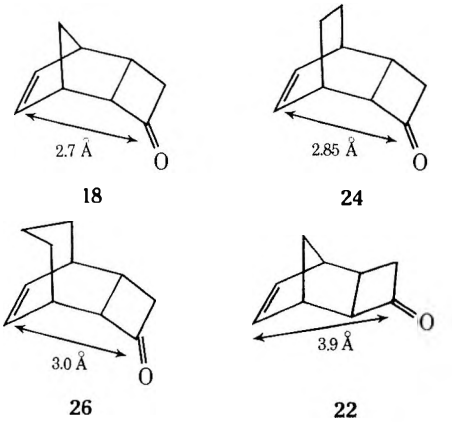
33 whose spectral properties were identical with those described by Sauers and co-workers.[16] In addition, the spectral properties of **22** were identical with those of a sample prepared in low yield by the addition of dichloroketene to norbornadiene to yield **34** and subsequent dechlorination.[2d,e] Since we had both isomers **18** and **22** in hand, we



33 **34** **35**

were able to verify by GLC analysis that the cycloaddition to norbornadiene and subsequent dechlorination produces >98% of the exo isomer which agrees with the results obtained by other workers by indirect analysis.[2e] The ketones **18** and **22** were further related to each other by photochemical transformation (300 nm) to the same ester, **35,** upon quenching with methanol after irradiation.[17]

Spectral Interaction. Spectral interaction between formally nonconjugated chromophores has been widely studied and found to be strongly geometry dependent.[18] The series of cyclobutanones **18, 22, 24,** and **26** by virtue of their structural rigidity provided an interesting series for a study of nonconjugated interaction as a function of geometry and distance between interacting centers (see below).



18 **24**

26 **22**

The shape and intensity of the n–π^* transition is remarkably similar for all of the polycyclic cyclobutanones with the exception of **22**, which is anomalous in that the extinction coefficient of the major vibrational component is ca. three times that of the other ketones and slightly red shifted (see paragraph at end of paper regarding supplementary material). That this striking intensification is caused by the presence of the double bond is clear from the spectrum of the saturated compound **33** which closely resembles the other derivatives. The distance between the chromophores in **22** is ca. 3.9 Å from models, which seems excessive for a simple through-space interaction. The n–π^* enhancement therefore seems best explained by chromophore interaction via the exo σ bond. Similar geometry dependent n–π^* enhancements of some polycyclic ketones have been reported recently by Hudec and co-workers.[19] These workers, however, also reported the presence of a short-wavelength σ coupled transition in the examples showing n–π^* intensification. We were unable to see any evidence of another maximum above 210 nm which could be ascribed to a σ coupled transition. The question of ground-state nonconjugated interactions in these and related systems is under investigation by photoelectron spectroscopy.

Summary

We have described a simple procedure for preparing 2,3-cis fused polycyclic cyclobutanones[20] on a preparative scale from available precursors which has provided a valuable complement to the use of dichloroketene in cyclobutanone synthesis. It has not only provided a high-yield synthesis of a number of ketones where the yield via dichloroketene was low but in addition has provided the complimentary endo isomers, **18, 20, 25,** and **26,** in cases where dichloroketone addition has been demonstrated or predicted to occur stereospecifically to produce the exo isomers. Further work on the chemistry of these and other related polycyclic cyclobutanones is proceeding.

Experimental Section[21]

***cis*-1,2-Dicarboethoxycyclohex-4-ene (1).** A 2-l. one-necked flask was charged with 100 g (0.66 mol) of *cis*-1,2,3,6-tetrahydrophthalic anhydride, 200 ml of anhydrous ethanol, 500 ml of dry benzene, and 2 ml of concentrated sulfuric acid. The mixture was refluxed for 16 h employing a Soxhlet extraction apparatus where the cup of the extractor was filled with activated 4 Å molecular sieves. The mixture was cooled and the solvent removed on a rotary evaporator. The residue was poured into a mixture of 200 ml of 10% salt solution and 400 ml of 5% sodium bicarbonate and extracted with ether. The organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent and vacuum distillation yielded 1 as a main fraction [bp 112–114 °C (1 mm), 140 g, 95%].

7,8-Bis(trimethylsiloxy)bicyclo[4.2.0]octa-3,7-diene (2). This general procedure was followed for all acyloin condensations. Into a flamed 2-l. four-necked flask equipped with a Hershberg stirrer, addition funnel, argon gas inlet, and condenser with drying tube were placed 9.2 g (0.4 mol) of sodium and 200 ml of dry toluene. The mixture was heated to reflux and stirred rapidly for 0.5 h to disperse the sodium before cooling to room temperature. A mixture of 20.0 g (0.089 mol) of *cis*-1,2 dicarboethoxycyclohex-4-ene (1) and 45.6 g (0.42 mol) of distilled trimethylsilyl chloride in 50 ml of toluene was added dropwise over 3 h. After the addition, the mixture was *carefully*[22] heated to reflux for an additional 12 h. A blue-violet color developed soon after the heating was begun. After the reaction mixture was cooled to room temperature, the precipitate was removed by filtration through Celite. The toluene was removed under reduced pressure (45 mm) and the residue was pumped to 0.2 mm for 10 min at 0 °C to remove the last remnants of the solvent. The residue was distilled through a 6-in. Vigreux column to yield the disiloxene, **2,** as the major fraction [bp 80–81°C (0.35 mm), 21.9 g 88%]: NMR ($CDCl_3$) τ 4.40 (m, 2 H), 7.40 (m, 2 H), 7.96 (m, 4 H), and 9.83 (s, 18 H); ir (neat 3050, 2950, 2900, 2850, 1720, 1310, 1280, 1250, 1220, 1120, 1050, 970, 915, 890, 850, 760, and 680 cm^{-1}; mass spectroscopic molecular weight 282.

7-Acetoxybicyclo[4.2.0]oct-3-en-8-one (15). A. The following general procedure for hydrolysis and acetylation was used except where noted. A 1-l. three-necked flask equipped with a stirrer, N_2 inlet, and condenser was charged with 66.7 g (0.24 mol) of **2,** 220 ml of THF, and 17.3 g of 1 N HCl. The mixture was refluxed under N_2 for 1 h. After cooling to room temperature, 17.3 g (0.17 mol) of $CaCO_3$ was added and the mixture stirred at room temperature for an additional 1 h. After filtration the THF was removed on the rotary evaporator and the crude product was dissolved in 175 ml of ether which was washed with water and dried over Na_2SO_4. Removal of the ether yielded 24.5 g (0.2 mol) of the yellowish oily acyloin.

B. The above acyloin was placed in a 250-ml flask immersed in a water bath (25 °C) and 55.8 ml (0.60 mol) of acetic anhydride and 16 ml (0.20 mol) of dry pyridine were added. The reaction was stirred at room temperature for 16 h. After the addition of 100 ml of water, the initial two-phase system was stirred for 1 h and the aqueous layer extracted repeatedly with ether. The organic phase was carefully washed with saturated $NaHCO_3$ and water and dried over Na_2SO_4. The product was isolated by distillation through a 6-in. Vigreux column to yield 27.4 g [bp 80–85 °C (0.04 mm), 77%] of the desired keto acetate, **15.** GLC analysis on column 1 operated at 120 °C with flow of 35 ml/min showed the presence of two isomeric acetates in the ratio of 1/4: NMR (CCl_4) τ 4.04–4.48 (m, 2.8 H), 5.05 (dd, J = 6, 2 Hz, 0.2 H), 6.51–7.06 (m, with two sharp singlets at 7.95 and 7.98, 9 H); ir (neat 3030, 2930, 2840, 1775, 1740, 1650, 1370, 1225, and 665 cm^{-1}.

The major keto acetate could be separated by GLC using column 2 at 130 °C and a flow rate of 60 ml/min: NMR (CCl_4) τ 4.22–4.46 (m, 3 H), 6.56–7.14 (m with sharp singlet at 7.95, 9 H); ir (neat) 3030, 2930, 2840, 1775, 1740, 1650, 1370, 1225 and 665 cm^{-1}. The minor acetate which was enriched to ca. 50/50 during collection showed similar spectral properties. The low-field portion of its NMR spectrum was, however, somewhat different from that of the major isomer in that the vinyl protons appeared as a multiplet at τ 4.03 while the cyclobutyl methine proton adjacent to the acetate group appeared upfield as a doublet of doublets (J = 6, 2 Hz) at τ 5.05.

Bicyclo[4.2.0]oct-3-en-7-one (16). The following general procedure was followed for all reductive deacetylations. A 2-l. three-necked flask equipped with a mechanical stirrer and nitrogen inlet was charged with 14.3 g (0.08 mol) of the keto acetate mixture **15,** 350 ml of glacial acetic acid, and 155 g (2.38 mol) of Zn dust. The reaction mixture was heated at reflux with vigorous stirring for 30 h. After this time >95% of the starting material had disappeared by GLC analysis (column 1, 150 °C, 35 ml/min). The reaction mixture was cooled and filtered, and the solid was washed with ether and poured into 350 ml of H_2O. The aqueous layer was extracted with ether which was washed with saturated $NaHCO_3$ and water and dried over Na_2SO_4. The ether was removed by distillation at 1 atm and the residue distilled under vacuum through a 6-in. Vigreux column. The main fraction [bp 94–96 °C (27 mm), 7.0 g, 72%] was >97% pure by GLC analysis (column 1, 86 °C, 35 ml/min): NMR (CCl_4) τ 4.23 (m, 2 H), 6.5–7.12 (m, 2 H), 7.15–8.22 (m, 6 H); ir (neat) 3035, 2920, 2840, 1775, 1640, 1435, 1385, 1265, 1225, 1105, 1085, 1010, and 680 cm^{-1}; mass spectroscopic molecular weight, calcd for $C_8H_{10}O$, 122.073; found, 122.074.

Hydrogenation of 16. The hydrogenation of **16** (182 mg, 1.49 mmol, PtO_2) in 10 ml of hexane was interrupted after an uptake of 97% of 1 equiv. The solvent was removed by distillation and the material collected by GLC (column 2, 110 °C, 80 ml/min). The spectral properties of the bicyclo[4.2.0]octan-7-one prepared in this manner were identical with those reported by Blomquist and Kwiatek:[12] NMR (CCl_4) τ 6.30–6.91 (m, 2 H) and 7.10–8.91 (m, 10 H); ir (neat) 2900, 2800, 1770, 1420, 1090, 1060, and 1040 cm^{-1}; mass spectroscopic molecular weight 124.

Irradiation of 16 to 1,4-Cyclohexadiene and 3-Norcarene. Into a Pyrex tube was placed 251 mg of **16** in 30 ml of pentane and the solution was degassed for 10 min with nitrogen. The sample was irradiated for 5 h at 300 nm. GLC (column 1, 85 °C, 30 ml/min) and spectral analysis showed that the starting material had been consumed and 1,4-cyclohexadiene and 3-norcarene had been formed in 58 and 13% yields, respectively.

***endo*-2,3-Dicarbomethoxybicyclo[2.2.1]hept-5-ene (3).** This material was prepared in 88% yield by the method described by Morgan and co-workers:[23] NMR (CCl_4) τ 3.92 (m, 2 H), 6.53 (s, 6 H), 6.8–7.05 (m, 4 H), and 8.78 (AB q, J = 9 Hz, 2 H); ir (neat) 2980, 2950, 1740, 1440, 1340, 1250, 1195, and 1165 cm^{-1}.

***endo*-3,4-Bis(trimethylsiloxy)tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (4).** Following the general procedure, **4** was obtained in 80%

yield, bp 78–81 °C (0.05 mm). A small higher boiling fraction, bp 100–105 °C (0.045 mm), proved to be a complex mixture and was discarded. GLC analysis of the major fraction (column 1, 155 °C, 35 ml/min) showed that it was >98% pure: NMR ($CDCl_3$) τ 4.2 (t, J = 1.5 Hz, 2 H), 7.38 (br d, J = 3 Hz, 2 H), 7.51 (m, 2 H), 8.37 (AB q, J = 8.5 Hz, 2 H), and 9.90 (s, 18 H); ir (neat) 3060, 2960, 1705, 1300, 1250, 1210, 1170, 1085, 966, 900, 840, and 730 cm^{-1}; mass spectroscopic molecular weight 294.

Irradiation of 4 to 4,5-Bis(trimethylsiloxy)homocubane (13). A Vycor tube (33 × 3.8 cm) was charged with 11.05 g (0.038 mol) of freshly distilled **4** dissolved in 250 ml of dry spectrograde cyclohexane (0.15 M). The tube was sealed with a syringe stopper and degassed with a stream of dry nitrogen. The solution was irradiated at 254 nm (Southern New England Ultraviolet Co., RPR-208) for 48 h. After removal of the solvent, the mobile yellowish residue was distilled through a 6-in. vacuum-jacketed Vigreux column to yield 9.24 g [bp 85–88 °C (0.12 mm), 84%] of the cage compound **13:** NMR (CCl_4) τ 6.85 (s, $W_{1/2}$ = 2.3 Hz, 6 H), 8.22 (s, $W_{1/2}$ = 2.7 Hz, 2 H), and 9.75 (s, 18 H); ir (neat) 2980, 1355, 1305, 1255, 930, 095, 875, and 840 cm^{-1}; mass spectroscopic molecular weight 294.

***endo*-3-Acetoxytricyclo[4.2.1.$0^{2,5}$]non-7-en-4-one (17).** The generalized procedure for hydrolysis and acetylization of the disiloxenes was followed and the keto acetate **17** was obtained in 60% yield (>98% pure, GLC analysis, column 1, 170 °C, 35 ml/min): bp 88–93 °C (0.04 mm); NMR (CCl_4) τ 3.97 (m, 2 H), 4.68 (dd, J = 8.5, 3.5 Hz, 1 H), 6.25–7.0 (m, 4 H), 7.97 (s, 3 H), 8.37 (AB q, J = 9 Hz, 2 H); ir (neat) 3060, 2975, 2860, 1780, 1740, 1370, 1225, 1025, 910, and 725 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.59; H, 6.44.

***endo*-Tricyclo[4.2.1.$0^{2,5}$]non-7-en-3-one (18).** Following the general procedure, the ketone **18** was generated as a waxy semisolid [bp 104–106 °C (33 mm), 66%]. The material was >95% pure by GLC analysis (column 1, 105 °C, 35 ml/min): NMR (CCl_4) τ 3.92 (t, J = 2.0 Hz, 2 H), 6.37 (m, 1 H), 6.97 (m, 2 H), 7.10–7.54 (m, 2 H), 7.76–8.1 (m, 1 H), and 8.43 (AB q, J = 9 Hz, 2 H); ir (CCl_4) 3060, 1985, 2870, 1775, 1640, 1280, 1335, 1250, 1170, 1085, and 715 cm^{-1}; mass spectroscopic molecular weight 134.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.73; H, 7.63.

***endo*-2,3-Dicarbomethoxybicyclo[2.2.1]heptane (5).** *endo*-Bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride (67 g) was dissolved in 150 ml of dry methanol containing 1 g of *p*-toluenesulfonic acid monohydrate. The homogeneous mixture was refluxed under nitrogen for 12 h. After cooling, the solvent was removed on the rotary evaporator and the residue dissolved in ether. The ether was washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. After removal of the solvent the residue was vacuum distilled to yield 78.2 g of ester **5** [bp 112–115 °C (2.5 mm), 91%]: mp 52.5–53.5 °C; NMR ($CDCl_3$) τ 6.33 (s, 6 H), 7.0 (m, 2 H), 7.42 (m, 2 H), 7.91–8.78 (m, 6 H).

***endo*-3,4-Bis(trimethylsiloxy)tricyclo[4.2.1.$0^{2,5}$]non-3-ene (6).** Following the general procedure, **6** was obtained in 90% yield: bp 84–85 °C (0.06 mm); NMR ($CDCl_3$) τ 7.4 (m, 2 H), 7.95 (m, 2 H), 8.45 (m, 2 H), 8.6 (m, 4 H), and 9.88 (s, 18 H); ir (neat) 2920, 2850, 1710, 1300, 1250, 1280, 1180, 1090, 985, 960, 890, 850, and 755 cm^{-1}; mass spectroscopic molecular weight 296.

***endo*-3-Acetoxytricyclo[4.2.1.$0^{2,5}$]nonan-3-one (19).** According to the usual procedure, the keto acetate **19** was obtained as a slightly pink liquid in 60% yield: bp 85–90 °C (0.08 mm); NMR ($CDCl_3$) τ 4.3 (dd, J = 9, 3 Hz, 1 H), 6.36–7.15 (m, 2 H), 7.45 (m, 2 H), 7.90 (s, 3 H), and 8.4 (m, 6 H); ir (neat) 2910, 2860, 1775, 1740, 1370, 1220, 1120, 1030, and 930 cm^{-1}.

***endo*-Tricyclo[4.2.1.$0^{2,5}$]nonan-3-one (20).** A. The ketone **20** was prepared using the general procedure for reductive deacetylation. GLC analysis (column 1, 151 °C, 35 ml/min) indicated olly 50% conversion after 23 h. The heating was continued for an additional 16 h after which the reaction was terminated despite the presence of ca. 30% starting material by GLC analysis. Work-up in the usual fashion and vacuum distillation yielded the ketone **20** as a waxy semisolid (bp 110–112 °C, 33 mm) and recovered starting material (bp 85–90 °C, 0.08 mm). The yield of **20** based on reacted starting material was 69%: NMR (CCl_4) τ 6.48 (m, 1 H), 7.0–7.3 (m, 5 H), and 8.41 (m, 6 H); ir (CCl_4) 2960, 2890, 1775, and 1090 cm^{-1}; mass spectroscopic molecular weight, calcd for $C_9H_{12}O$, 136.089; found, 136.091.

B. Hydrogenation of 18. The ketone **18** (2.0 g, 14.9 mol) was hydrogenated at 1 atm in hexane containing 100 mg of PtO_2. The hydrogenation was interrupted after the uptake of 97% of the theoretical amount of hydrogen. The catalyst was removed and the hexane distilled at 1 atm. The product distilled under vacuum to yield 1.8 g of the desired ketone **20.** The physical and spectral properties were identical with those prepared by procedure A.

***exo*-2,3-Dicarbomethoxybicyclo[2.2.1]hept-5-ene (7).** This material was prepared from *exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride[24] according to the procedure described for the preparation of **3:** mp 50–52 °C; NMR ($CDCl_3$) τ 4.79 (t, J = 2 Hz, 2 H), 6.34 (s, 6 H), 6.90 (m, 2 H), 7.36 (d, J = 2 Hz, 2 H), 8.15 (AB q, J = 8.5 Hz, 2 H); ir 3050, 1740, 1430, 1360, 1330, 1250, 1140, 1160, 1050, and 740 cm^{-1}.

***exo*-3,4-Bis(trimethylsiloxy)tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (8).** Using the generalized procedure, the disiloxene derivative **8** was obtained in 75% yield: bp 78–85 °C (0.05 mm); NMR ($CDCl_3$) τ 3.90 (t, J = 2 Hz, 2 H), 5.51 (m, 2 H), 7.82 (s, 2 H), 8.48 (AB q, J = 9 Hz, 2 H), and 9.8 (s, 18 H); ir 3060, 1710, 1310, 1300, 1270, 1250, 1200, 1180, 1095, 945, 910, 880, 850, 760, and 710 cm^{-1}; mass spectroscopic molecular weight 294.

***exo*-3-Acetoxytricyclo[4.2.1.$0^{2,5}$]non-7-en-3-one (21).** Into a 250-ml flask equipped with a condenser and positive pressure N_2 bubbler was placed 19.0 g (0.065 mol) of **8** and 100 ml of methanol distilled from magnesium. The mixture was heated to reflux for 3 h and the solvent was removed on the rotary evaporator at 50 °C. The residue (9.0 g) solidified upon standing. The crude acyloin was treated with 17 ml (0.18 mol) of acetic anhydride and 4.84 ml (0.06 mol) of dry pyridine while maintaining ambient temperature with an external water bath. The dark solution was stirred at room temperature for 16 h and worked up according to the procedure described for the preparation of **13.** Vacuum distillation yielded 8.0 g of the keto acetate **21** [bp 93–96 °C (0.05 mm), 65%]. The pinkish distillate partially solidified in the freezer at −10 °C overnight: mp 42.5–43 °C (hexane); NMR ($CDCl_3$) τ 3.75 (m, 2 H), 4.43 (dd, J = 9, 3.5 Hz, 1 H), 6.64–7.32 (m, 2 H), 7.90 (s, 3 H), and 8.46 (AB q, J = 9.5 Hz, 2 H); ir (neat) 3050, 3000, 2990, 1780, 1740, 1280, 1230, 1100, 903, and 708 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.84; H, 6.37.

***exo*-Tricyclo[4.2.1.$0^{2,5}$]non-7-en-3-one (22).** Application of the usual procedure for reductive elimination yielded the ketone **22** in 76% isolated yield: bp 105–106° (30 mm); NMR ($CDCl_3$) τ 3.80 (m, 2 H), 6.76–7.08 (m, 3 H), (m, 3 H), and 8.48 (m, 2 H); ir (neat) 3070, 3000, 2900, 1775, 1090, 732, and 690 cm^{-1}; mass spectroscopic molecular weight 134.

3,3-Dichlorotricyclo[4.2.1.$0^{2,5}$]non-7-en-4-one (34). A dry 1-l. three-necked flask equipped with a mechanical stirrer, N_2 inlet, and condenser was charged with 30.0 g (0.20 mol) of freshly distilled dichloroacetyl chloride, 181.1 g (2.05 mol) of norbornadiene, and 250 ml of pentane (distilled from CaH_2). A solution of dry triethylamine (21.39 g, 0.21 mol) in 50 ml of pentane was slowly added. The reaction mixture was stirred for 15 h at room temperature after the addition. After filtering, the low boilers were removed on the rotary evaporator at 45 °C and the residue vacuum distilled. The product which distilled as the major fraction [bp 60–61 °C (0.14 mm), 6.77 g, 17.5%] was slightly yellow. Owing to the limited stability of the dichlorocyclobutanone it was always used soon after preparation: NMR ($CDCl_3$) τ 3.82 (m, 2 H), 6.45 (doublet split into triplets, J = 6.5, 1.5 Hz, respectively), 6.77 (m, 1 H), 7.13 (dd, J = 6.5, 1.0 Hz, 1 H), and 8.47 (m, 2 H); ir (neat) 3070, 2970, 2860, 1785, 1656, 1310, 1010, 970, 822, 743, and 710 cm^{-1}.

Alternate Preparation of 22. A 500-ml flask was charged with 8.40 g (0.041 mol) of dichlorocyclobutanone **34,** 54.3 (0.83 mol) of Zn dust, and 250 ml of acetic acid. The mixture was heated to reflux with vigorous stirring for 2 h. The reaction mixture was worked up in the same manner as described for the preparation of **14.** Vacuum distillation yielded the product **22** (bp 85–88 °C, 15 mm) in 76% yield. The spectral data were identical with those previously described.

Hydrogenation of 22. The ketone **22** (235.5 mg, 1.76 mmol) was hydrogenated in hexane over 50 mg of PtO_2 at 1 atm. The reduction was interrupted after the consumption of 1.05 equiv of hydrogen. The catalyst was filtered and the hexane removed using a 6-in. glass helice packed column. The product, **33,** was isolated (85%) by gas chromatography (column 2, 145 °C, 60 ml/min). The spectral data of this material were identical with those reported by Sauers and co-workers:[16] NMR (CCl_4) τ 6.82–7.20 (m, 2 H), 7.39–7.97 (m, 4 H), and 8.22–9.06 (m, 6 H); ir (CCl_4) 2920, 2840, 1775, and 1093 cm^{-1}; mass spectroscopic molecular weight 136.

***endo*-2,3-Dicarbomethoxybicyclo[2.2.2]oct-5-ene (9).** The ester **9** was prepared from *endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicar-

boxylic anhydride[25] using the procedure previously described for the preparation of **3**. The crude ester was recrystallized from ether to yield the pure dimethyl ester **9**, mp 68–69 °C (lit.[26] 69–71 °C).

***endo*-3,4-Bis(trimethylsiloxy)tricyclo[4.2.2.0^{2,5}]deca-3,7-diene (10).** Using the generalized procedure described for the preparation of the disiloxenes, **10** was generated in 83% yield (bp 85–89 °C, 0.012 mm). The product after one distillation was >98% pure by GLC analysis (column 1, 170 °C, 35 ml/min): NMR ($CDCl_3$) τ 4.10 (m, 2 H), 7.25–7.9 (m, 4 H), 8.6 (m, 4 H), 9.8 (s, 18 H); ir (neat) 3040, 2940, 2840, 1710, 1310, 1250, 915, 875, and 840 cm^{-1}; mass spectroscopic molecular weight 306.

Irradiation of 10 to Yield 14. The disiloxene derivative **10** (1.0 g, 3.24 mmol) was dissolved in 30 ml of spectrograde cyclohexane and placed in a Vycor tube. The tube was degassed, sealed, and irradiated at 254 nm (as described for **13**) for 48 h. The solvent was removed at reduced pressure and the residue distilled through a molecular still (bath 150 °C, 0.017 mm) to yield 60 mg of a colorless liquid. The cage compound **14** was collected (column 2, 160 °C, 60 ml/min) to yield 40 mg of **14**: NMR (CCl_4) τ 7.17–7.55 (m, 6 H), 8.70 (m, $W_{1/2}$ = 4 Hz, 4 H), and 9.8 (s, 18 H); ir (neat) 2950, 2920, 1355, 1340, 1290, 1250, 900, 860, and 830 cm^{-1}; mass spectroscopic molecular weight 306.

***endo*-3-Acetoxytricyclo[4.2.2.0^{2,5}]dec-7-en-4-one (23).** The keto acetate **23** was prepared from **10** by the usual procedure. Vacuum distillation yielded 25.6 g (84% from **10**) of **23** [slightly pink, bp 108–112 °C (0.17 mm)]. The distilled material was 98% pure by GLC analysis (column 1, 180 °C, 35 ml/mm). A sample was crystallized from hexane to yield white crystals: mp 49–51 °C; NMR ($CDCl_3$) τ 3.90 (m, 2 H), 4.54 (dd, J = 9, 4 Hz, 1 H), 6.40–7.46 (m, 4 H), 7.96 (s, 3 H), and 8.97 (m, 4 H); ir (neat) 3050, 2940, 2870, 1780, 1735, 1370, 1220, 1025, and 700 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.74; H, 6.80.

***endo*-Tricyclo[4.2.2.0^{2,5}]dec-7-en-3-one (24).** The tricyclic ketone was produced by the general procedure in 77% yield: bp 116–120 °C (16 mm); NMR (CCl_4) τ 3.82 (m, 2 H), 6.74 (m, 1 H), 6.93–7.81 (m, 5 H), and 8.39–8.87 (m, 4 H); ir (CCl_4) 3050, 2910, 2820, 1775, 2380, 1220, 1100, 850, and 722 cm^{-1}; mass spectroscopic molecular weight 148.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04, H, 8.16. Found: C, 80.81; H, 8.31.

***endo*-2,3-Dicarboethoxybicyclo[3.2.2]non-5-ene (11).** *endo*-Bicyclo[3.2.2]non-5-ene-2,3-dicarboxylic anhydride (15.0 g, 0.078 mol)[27] was placed in a 1-l. flask with 100 ml of anhydrous ethanol, 300 ml of benzene, and 1 ml of concentrated sulfuric acid. The flask was attached to a Soxhlet extractor containing 4 Å molecular sieves in the cup and refluxed for 3 days. The clear reaction mixture was cooled and poured into a mixture of 100 ml of 10% NaCl and 300 ml of 5% $NaHCO_3$ solution. The layers were separated and the organic layer washed several times with water. After drying over Na_2SO_4 the solvent was removed on the rotary evaporator. Vacuum distillation of the residue yielded 19.43 g of the desired ester, **11** [bp 108–110 °C (0.04 mm), 93%]: NMR (CCl_4) τ 4.0 (m, 2 H), 6.02 (q, J = 7 Hz, 4 H), 6.94 (s, 2 H), 7.0–7.32 (m, 2 H), 8.1–8.6 (m, 6 H), and 8.8 (t, J = 7 Hz, 6 H); ir (neat) 3040, 2980, 2940, 2860, 1745, 1180, 1155, 1055, and 705 cm^{-1}.

***endo*-3,4-Bis(trimethylsiloxy)tricyclo[4.3.2.0^{2,5}]undeca-3,10-diene (12).** Application of the usual procedure produced **12** in 81% yield: bp 100–104 °C (0.06 mm); NMR (CCl_4) τ 4.26 (m, 2 H), 7.44 (s, 2 H), 7.56–7.88 (m, 2 H), 8.15–8.92 (m, 6 H), and 9.80 (s, 18 H); ir (neat) 3040, 2960, 2910, 2850, 1715, 1310, 1285, 1250, 1200, 910, 880, and 840 cm^{-1}; mass spectroscopic molecular weight 322.

***endo*-4-Acetoxytricyclo[4.3.2.0^{2,5}]undec-10-en-3-one (25).** Following the general procedure, **25** was generated in 90% yield: bp 124–130 °C (0.09 mm); NMR (CCl_4) τ 4.04 (m, 2 H), 4.47 (dd, J = 9, 3.5 Hz, 1 H), 6.53–7.00 (m, 2 H), 7.3 (br m, 1 H), 7.6 (br m, 1 H), 8.02 (s, 3 H), and 8.28–8.67 (m, 6 H); ir (neat) 3043, 2935, 2860, 1786, 1740, 1240, 1233, and 708 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.47; H, 7.29.

***endo*-Tricyclo[4.3.2.0^{2,5}]undec-10-en-3-one (26).** The ketone **26** was prepared from **25**, using the general procedure described previously. After 22.5 h, GLC analysis (column 1, 177 °C, 35 ml/min) showed no more starting material present. Work-up in the usual manner and vacuum distillation yielded **26** [bp 85–86 °C (1.0 mm), 76.4%]: NMR (CCl_4) τ 4.92 (m, 2 H), 6.54 (m, 1 H), 6.80–7.63 (m, 5 H), and 8.0–8.62 (m, 6 H); ir (neat) 3030, 2929, 2850, 1775, 1380, 1090, and 708 cm^{-1}; mass spectroscopic molecular weight, calcd for $C_{11}H_{14}O$, 162.104; found, 162.104.

Baeyer–Villiger Oxidation of 18. A 50-ml flask was charged with 134 mg (1 mmol) of **18**, 7 ml of MeOH, and 306 mg (30%) of H_2O_2 at ambient temperature. Then 0.14 ml of 9.3 N sodium hydroxide solution was added while maintaining room temperature with a water bath. The reaction mixture was stirred for 2.5 h at room temperature and diluted with 17 ml of 10% HCl solution. The aqueous solution was extracted four times with 20 ml of ether. After drying (Na_2SO_4) the solvent was removed to yield 90 mg (60%) of a crude lactone mixture. A single peak was observed by GLC (column 1, 125 °C, 35 ml/min). However, on column 3, 160 °C, 60 ml/min, the lactones were separated (32% **27**, 68% **28**). The lactones were collected from column 4 at 175 °C, 60 ml/min.

Lactone **27**: NMR (CCl_4) τ 3.81 (m, 2 H), 5.03 (dd, J = 8, 4 Hz, 1 H), 6.87 (br m, 1 H), and 6.9–8.78 (complex multiplet containing an AB q centered at τ 8.5, J = 9 Hz, 6 H); ir (CCl_4) 3065, 2900, 2880, 1770, 1355, 1160, 1070, 1055, and 1010 cm^{-1}; mass spectroscopic molecular weight 150.

Lactone **28**: NMR (CCl_4) τ 3.80 (br s, 2 H), 5.67–5.92 (m, 1 H), 6.20–6.43 (m, 1 H), 6.67–7.65 (m, 4 H), and 8.44 (AB q, J = 9 Hz, 2 H); ir (CCl_4) 3070, 2980, 2920, 2880, 1770, 1385, 1300, 1175, 1090, 1060, 1100, and 925 cm^{-1}; mass spectroscopic molecular weight 150.

Baeyer–Villiger Oxidation of 24. The same procedure run on a 1-mmol scale was used as described for the oxidation of **18**. After the usual work-up, 125 mg (76%) of the lactone mixture was obtained. GLC analysis (column 1, 140 °C, 35 ml/min) showed two lactones present in the ratio 1.3/1. The lactones were collected from column 4, 175 °C, 60 ml/min. The major lactone (54%) was identified as **30** and the minor (46%) as **29**.

Lactone **29**: NMR ($CDCl_3$) τ 3.70 (m, 2 H), 5.30 (dd, J = 8.3, 3 Hz, 1 H), 7.0 (m, 2 H), and 7.16–8.9 (complex multiplet, 7 H); ir (KBr) 2900, 1770, 1190, 1040, 1030, 1010, 880, 730, and 690 cm^{-1}; mass spectroscopic molecular weight 164.

Lactone **30**: NMR ($CDCl_3$) τ 3.72 (m, 2 H), 5.4–5.87 (m, 1 H), 6.00–6.35 (m, 1 H), 6.77–7.50 (m, 4 H), and 8.3–9.0 (m, 4 H); ir (CCl_4) 2900, 1770, 1180, 1050, and 1010 cm^{-1}; mass spectroscopic molecular weight 164.

Baeyer–Villiger Oxidation of 26. The procedure for preparation and collection was that described above. From 1 mmol of **26** was obtained 152 mg of a 1/2.8 mixture (column 1, 140 °C, 35 ml/min) of lactones **32** and **31**, respectively.

Lactone **31**: NMR (CCl_4) τ 3.88 (m, 2 H), 5.2 (m, 1 H), 7.0–8.0 (m, 5 H), and 8.42 (m, 6 H); ir (CCl_4) 3040, 2930, 2860, 1780, 1020, and 710 cm^{-1}; mass spectroscopic molecular weight 178.

Lactone **32**: NMR (CCl_4) τ 3.83 (m, 2 H), 5.62 (t, J = 9 Hz, 1 H), 6.28 (dd, J = 9, 4 Hz, 1 H), 6.85–7.29 (m, 3 H), 7.62 (m, 1 H), 8.05–8.58 (m, 6 H); ir (CCl_4) 3040, 2930, 2920, 2860, 1773, 1185, 1170, 1050, 1030, and 710 cm^{-1}; mass spectroscopic molecular weight 178.

Preparation of Lactone 28. The procedure followed was essentially that described by Bloomfield and Lee[14] using the following quantities: 16.4 g (0.1 mol) of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, 2.2 g (0.05 mol) of lithium aluminum hydride in 150 ml of THF at −55 °C. Work-up as described yielded 12.1 g of a viscous oil. This was dissolved in 30 ml of ether and cooled to −78 °C to force crystallization. In this way 10.3 g (69%, mp 125–130 °C) of a white, crystalline material was obtained. The spectral data of this lactone were identical with those of **28** produced by the Baeyer–Villiger oxidation of the ketone **18**.

Preparation of Lactone 30. The procedure followed was that described by Nystrom and Brown[28] using the following quantities: 4.8 g of *endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (0.03 mol) and 1.14 g (0.33 mol) of $LiAlH_4$ in 125 ml of ether. Work-up in the described fashion yielded 1.19 g (26%) of crystalline lactone from the reacidified basic extracts. This material was recrystallized from ether–pentane to yield a white, crystalline material, mp 86–88.5 °C, whose spectral data were identical in every way with those of **30** produced by Baeyer–Villiger oxidation of **24**.

Preparation of Lactone 32. The same procedure was followed as described for the preparation of **28** starting with *endo*-bicyclo-[3.2.2]non-8-ene-6,7-dicarboxylic anhydride. The crude product was distilled (bp 130–150 °C, 0.04 mm) using a 6-in. Vigreux column. The distillate was a mixture of the lactone **32** and the starting anhydride. The mixture was chromatographed on silica gel using 2% EtOAc–benzene to yield pure lactone **32**, whose spectral properties were identical with those produced by Baeyer–Villiger oxidation of **26**.

Irradiation of 18. Generation of 35. A solution of 200 mg of **18** in 40 ml of pentane (0.04 M) was placed in a Pyrex tube and degassed using N_2 for 15 min at room temperature. The tube was irradiated using a Southern New England Ultraviolet Rayonet reac-

tor and 300 nm lamps for 10 h. GLC analysis (column 1, 150 °C, 30 ml/min) showed that the starting material was gone. The solution was quenched with 1 ml of dry methanol and allowed to stand for 3 h at room temperature. The pentane was removed on the rotary evaporator after filtering to yield 162 mg (65%) of the ester **35** as a oil. This was further purified by GLC collection (column 2, 110 °C, 60 ml/min): NMR ($CDCl_3$) τ 3.93–4.43 (m, 3 H), 4.70–5.14 (m, 2 H), 6.24 (s, 3 H), 6.43–7.06 (m, 2 H), and 7.19–9.0 (m, 4 H); ir (neat) 3000, 2900, 2800, 1740, 1635, 1260, 1190, 1160, 1020, 995, 920, and 750 cm^{-1}; mass spectroscopic molecular weight 166.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26, H, 8.49. Found: C, 72.43; H, 8.26.

Irradiation of 22. The ketone **22** (32.9 mg) was dissolved in 12 ml of spectrograde pentane (0.02 M) and placed in a Pyrex tube. After degassing at 0 °C for 15 min the sample was irradiated as described above for 75 min. GLC analysis (column 1, 105 °C, 30 ml/min) indicated >95% consumption of starting material. The reaction was quenched with 0.5 ml of methanol added at room temperature. The major product (11%) was shown by GLC comparison and its spectral data to be the ester **35.**

Registry No.—**1,** 2305-26-2; **2,** 18014-24-9; **3,** 39589-98-5; **4,** 39762-43-1; **5,** 4098-47-9; **6,** 56514-07-9; **7,** 7184-07-8; **8,** 57819-09-7; **9,** 4545-84-0; **10,** 39762-44-2; **11,** 57774-80-8; **12,** 39762-45-3; **13,** 39873-35-3; **14,** 39762-46-4; **15a,** 57774-81-9; **15b,** 57819-10-0; **16,** 57774-82-0; **17,** 57819-11-1; **18,** 35150-63-1; **19,** 57774-83-1; **20,** 35150-65-3; **21,** 57819-12-2; **22,** 32166-31-7; **23,** 57774-84-2; **24,** 35237-74-2; **25,** 57774-85-3; **26,** 54566-00-6; **27,** 54566-21-1; **28,** 14315-51-6; **29;** 54566-22-2; **30,** 54595-30-1; **31,** 54566-24-4; **32,** 54566-25-5; **33,** 16529-77-4; **34,** 57774-86-4; **35,** 35150-66-4; *cis*-1,2,3,6-tetrahydrophthalic anhydride, 935-79-5; ethanol, 64-17-5; trimethylsilyl chloride, 75-77-4; *endo*-bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride 17812-27-0; methanol, 67-56-1; *exo*-bicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, 2746-19-2; dichloroacetyl chloride, 79-36-7; norbornadiene, 121-46-0; *endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride, 24327-08-0; *endo*-bicyclo[3.2.2]non-5-ene-2,3-dicarboxylic anhydride, 29577-71-7; lithium aluminum hydride, 16853-85-3.

Supplementary Material Available. The detailed ultraviolet spectra in the n–π^* region for compounds **16, 18, 20, 22, 26,** and **33** (1 page). Ordering information is given on any current masthead page.

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(20) This technique has also been used for preparing monocyclic cyclobutanones; e.g., a mixture of 2,2- and 3,3-dimethylcyclobutanone has been prepared in good yield from dimethyl 2,2-dimethylsuccinate in this manner (unpublished results).

(21) All melting and boiling points are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. NMR spectra were recorded on a Joelco Minimar, Varian HA-60-IL, or HA-100 instrument with Me_4Si as an internal standard. Infrared spectra were run on a Beckman 521 grating instrument or a Perkin-Elmer Infracord. The ultraviolet spectra were taken on a Cary 14 instrument. We thank Dr. S. Rottschaeffer of the University of Oregon for the high-resolution mass spectra. The analytical and preparative gas chromatography were done using a Hewlett-Packard Model 5750 instrument employing the following columns: column 1, 6 ft × 0.125 in., 10% UCW 98 on Chromosorb W (HMDCS); column 2, 6 ft × 0.25 in., 20% SE-30 on Chromosorb W (HMDCS); column 3, 10 ft × 0.125 in., 10% Carbowax 20M on Chromosorb P; column 4, 6 ft × 0.25 in., 10% Carbowax 20M on Chromosorb P.

(22) If all of the ester and trimethylsilyl chloride were added prior to heating, a strong exotherm was observed upon warming once the internal temperature reached ca. 70 °C. The exotherm is accompanied by the appearance of the blue-violet color. An alternative proceudre which can be employed involves adding the ester–trimethylsilyl chloride mixture slowly to the well-stirred sodium dispersion at 70 °C. Similar results were obtained for both procedures and the latter is more convenient for large runs.

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Syntheses and Chiroptical Properties of Optically Active Derivatives of Tricyclo[3.3.0.0^{3,7}]octane and Oxatricyclononanes[1]

Masao Nakazaki,* Koichiro Naemura, and Yasumasa Kondo

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan

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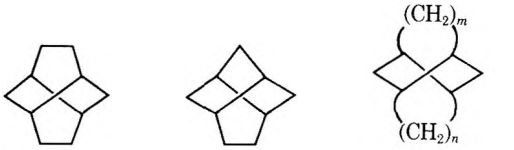
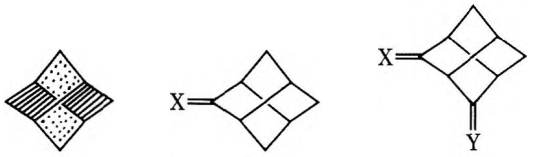
The optically active desymmetrized tricyclo[3.3.0.0^{3,7}]octane derivatives, (−)-4-methylenetricyclo[3.3.0.0^{3,7}]-octan-2-one (**20**) and (+)-4-isopropylidenetricyclo[3.3.0.0^{3,7}]octan-2-one (**21**), were prepared from (−)-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene (**14**) via optically active oxetane, (−)-2-methyl-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (**18**) and (−)-2-isopropyl-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (**24**), respectively. The syntheses established equivocally absolute configurations of these compounds, whose chiroptical properties are compared with those of tricyclo[4.4.0.0^{3,8}]decane ("twistane") and tricyclo[4.3.0.0^{3,8}]nonane ("twist-brendane") series of compounds. Oxatricyclononanes, 2-oxatricyclo[4.3.0.0^{4,8}]nonane (**7**) and 2-oxatricyclo[4.2.1.0^{4,8}]nonane (**8**), which have intrinsic chiral skeletons were also synthesized in optically active modifications.

In our preceding papers, syntheses of optically active tricyclo[4.4.0.0^{3,8}]decane[2c] ("twistane") and tricyclo[4.3.0.0^{3,8}]nonane[3c,3d] ("twist-brendane"), together with determinations of their absolute configurations, were reported; both (+)-twistane (D_2 point group) and (+)-twist-brendane (C_2 point group) can be represented by the formulas **1** and **2**, respectively.



1 **2** **3**

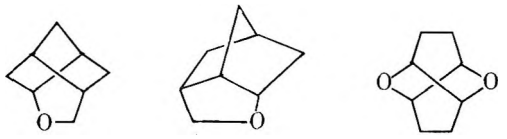


4 **5** **6**

Collectively, these compounds can be regarded to be constructed by freezing the cyclohexane ring in a chiral twist-boat conformation by means of two short bridges $(CH_2)_m$ and $(CH_2)_n$ spanning over C_1 and C_4 as well as C_2 and C_5 carbon atoms as shown in structure **3**. When both the two bridges become methylene groups, a new situation emerges affording achiral tricyclo[3.3.0.0^{3,7}]octane[5] ("bisnoradamantane")[6] (**4**). A noteworthy feature in this molecular system (D_{2d} point group) is the condensed ring system which complies two twist-boat cyclohexanes of opposite chiralities (the hatched and the dotted ones indicated in the formula **4**). Two methylene groups in the same twist-boat cyclohexane ring system are homotopic whereas those in different cyclohexanes are enantiotopic; i.e., they form two equivalent sets of enantiotopic methylene groups. This symmetric bisnoradamantane system can be desymmetrized by converting one of the enantiotopic methylene groups into sp^2 center (X) (**5**), and desymmetrization can also be achieved by conversion of the enantiotopic methylene groups into different sp^2 centers (X, Y) to give the compound **6**.

Comparison of these desymmetrized bisnoradamantane series of compounds with twistane, twist-brendane, and their derivatives possessing intrinsic chiral structures can be expected to reveal various interesting features. In this paper, we report the syntheses of some of the optically active desymmetrized bisnoradamantane derivatives together with their chiroptical properties.

The symmetry considerations can further be extended to 2-oxatricyclo[4.3.0.0^{4,8}]nonane[7] ("2-oxa-twist-brendane") (**7**) and 2-oxatricyclo[4.2.1.0^{4,8}]nonane[8] ("2-oxabrendane") (**8**). Having an intrinsic chiral skeleton, the compound **7** keeps the original chirality upon exchange of the heteroatom with the methylene group of **7**, whereas the compound **8** changes into the enantiomeric form upon the same transformation.



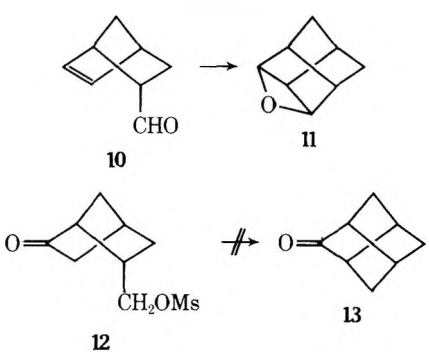
7 **8** **9**

Besides these interesting stereochemical aspects, their syntheses in optically active forms with known absolute configurations seems appropriate to be reported here, since (−)-2,7-dioxatwistane[9] (**9**) has been the sole optically active species belonging to this type of cage-shaped compound so far prepared.

Results and Discussion

Syntheses of Optically Active Bisnoradamantane Derivatives. Although the Paterno–Büchi photocyclization[5g,5h] has been proved successful to secure various cage-shaped compounds, unfortunately this route cannot be applied to the optically active unsaturated aldehyde **10** since the expected oxetane **11** turns out to be achiral (Scheme I).

Scheme I



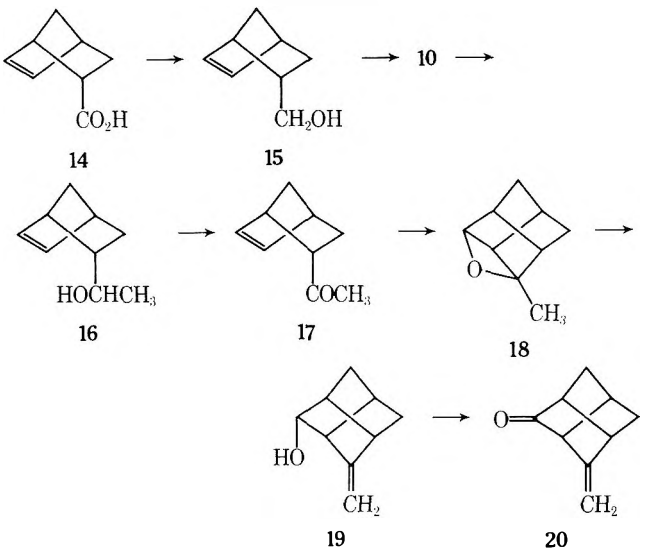
10 **11**

12 **13**

After a fruitless attempt to cyclize the mesylate **12** to tricyclo[3.3.0.0^{3,7}]octan-2-one (**13**), our efforts were directed toward the sequence illustrated in Scheme II.

(−)-*endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (**14**) with known absolute configuration[10] was reduced with lithium

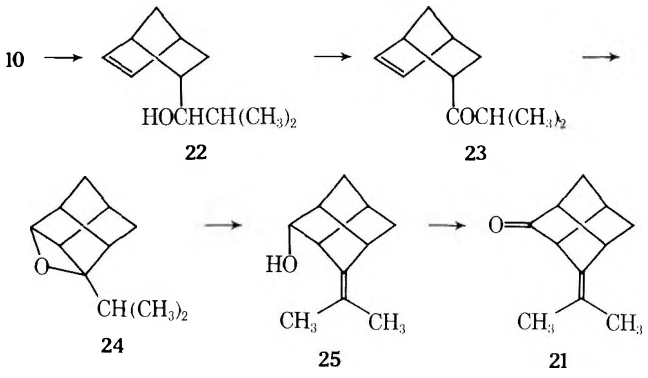
Scheme II



aluminum hydride to (−) unsaturated alcohol **15**, which was converted into the (−) unsaturated aldehyde **10** with Collins' reagent. Treatment with methylmagnesium iodide converted the (−) aldehyde **10** into the (−) alcohol **16**, which was oxidized to give (−) unsaturated methyl ketone **17**. A solution of **17** was irradiated with a medium-pressure mercury lamp to furnish (−)-2-methyl-3-oxatetracyclo-[4.2.1.$0^{2,5}$.$0^{4,8}$]nonane (**18**). Since cleavage of the oxetane ring with methanolic perchloric acid solution,[3b,3d] which has been so successful in the twist-brendane series of compound, failed, we treated **18** with hot lithium diethylamide[11] in a benzene solution to obtain alcoholic product (**19**), which was converted into 4-methylenetricyclo[3.3.0.$0^{3,7}$]-octan-2-one (**20**) upon oxidation with Collins' reagent. The structure was confirmed by infrared spectrum, exhibiting absorptions at 1765 (O=C) and at 1672, 835 cm^{-1} (H_2C=C), and NMR spectrum, which showed absorptions at δ 4.67 and 4.53 (olefinic protons).

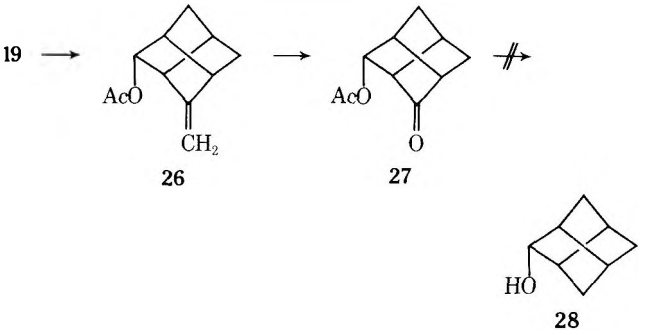
A similar sequence of transformations as shown in Scheme III converted **10** into (+)-4-isopropylidenetricyclo[3.3.0.$0^{3,7}$]octan-2-one (**21**).

Scheme III



Upon treatment with isopropylmagnesium bromide, the (−) aldehyde **10** afforded the (−) alcohol **22** which was oxidized to give the (−) ketone **23**. Photocyclization of **23** gave the (−) oxetane **24**, whose oxetane ring was cleaved to yield (+)-4-isopropylidenetricyclo[3.3.0.$0^{3,7}$]octan-2-ol (**25**) on treatment with lithium diethylamide. Oxidation of **25** with Collins' reagent gave **21** which showed absorption at 1755 cm^{-1} (O=C) in the infrared spectrum and proton signals at δ 1.64 (doublet) and 1.69 (doublet) due to the nonequivalent methyl groups in the NMR spectrum. Having secured these optically active ketones with known absolute configurations, our efforts were directed toward conversion of the disubstituted derivatives into the optically active monosubstituted derivative,[12] i.e., bisnoradamantanone (**13**). An obvious route would be the one starting from the unsaturated ketone **20**, but the compound **20** was found to suffer a deep-seated decomposition on Wolff-Kishner reduction. Therefore, we made a detour illustrated in Scheme IV. The

Scheme IV



acetate **26** was converted into the acetate-ketone **27** by ozone cleavage at −78 °C but again its Wolff–Kishner reduction was found to cause a deep-seated decomposition affording various cleavage products.

Syntheses of Optically Active Oxatricyclononanes. Synthesis of (−)-2-oxatricyclo[4.3.0.$0^{4,8}$]nonane (**7**) is rather straightforward. According to Kropp's procedure[7] to effect diagonal ring closing, the (−) unsaturated alcohol **15** was irradiated with a medium-pressure mercury lamp, and the product was purified by chromatography and sublimation affording **7** (Scheme V). This substance has a smell

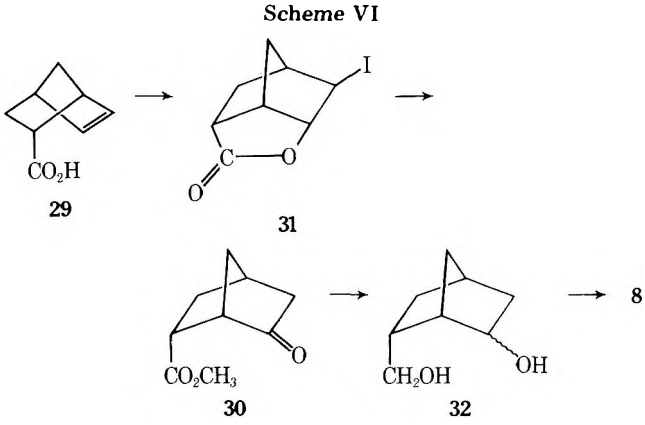
Scheme V

15 ⟶ 7

reminiscent of camphor, characteristic to cage-shaped hydrocarbons such as twistane and twist-brendane.

Our last efforts were directed toward the preparation of optically active 2-oxatricyclo[4.2.1.$0^{4,8}$]nonane (**8**) which is distinct from 2-oxa-twist-brendane (**7**) in regard to the direction of the ether bridging: diagonal in the former and transversal in the latter. Scheme VI depicts the synthetic

Scheme VI



route to (−)-2-oxabrendane (**8**) from (+)-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene (**29**). The (+) carboxylic acid **29** was converted into (+)-ketocarboxylic acid methyl ester (**30**) via iodolactone **31**[13] and the (+) ester **30** was reduced with lithium aluminum hydride to furnish the (−) diol **32** which was treated with *p*-toluenesulfonyl chloride in cold pyridine solution. From the pentane-soluble fraction was isolated the oxa derivative, whose infrared spectrum and NMR spectrum exhibited absorptions at 1080 cm^{-1} (ether

Table I. Specific Rotations of Bisnoradamantane Derivatives and Twist-Brendane Derivatives

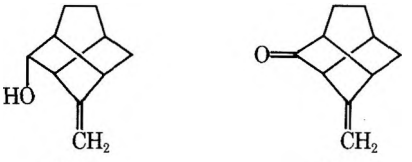
Compd	[α]D,[a] deg	Compd	[α]D,[a] deg
19	+13.2		
25	+18.3	**33**	−319
20	−36.6	**35**	−450
21	+37.6		

[a] Solvent ethanol.

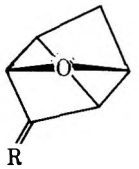
linkage) and at δ 4.20–4.42 (2 H, C_1 methylene protons), 3.65–3.90 (2 H, C_3 methylene protons), respectively. Besides obvious evidence from the synthetic route, their spectroscopic evidence clearly indicates the structure of 2-oxabrendane (**8**) for this compound.

Chiroptical Properties. As can be seen from Table I, which compared specific rotations of corresponding bisnoradamantane and twist-brendane series of compounds,[3c,3d] the bisnoradamantane series without intrinsic skeletal chirality always shows much smaller optical rotations. This is in harmony with our previously advanced explanation that a "twist" of the carbon skeleton mainly contributes to their optical rotation in these cage-shaped molecules.

In their circular dichroism curves, (−)-bisnoradamantanone with methylene group (**20**) exhibits maxima at 199.5 ([θ], $+9.8 \times 10^4$), 301 (-1.79×10^4), and 307 nm (sh) (-1.65×10^4); (+)-bisnoradamantanone with isopropylidene group (**21**) shows maxima at 214 ([θ], $+3.26 \times 10^4$), 298.5 (-1.37×10^4), and 304 nm (sh) (-1.34×10^4). The negative Cotton effect due to n–π* transition observed at around 300 nm can be explained just as in the case of twistanone and twist-brendanone: application of the octant rule to the projection formula **34** in which the carbonyl group is placed at the "point of twist".[14] In a previous paper,[3d] we indicat-



33 **35**



R = CH_2 or $C(CH_3)_2$

34

ed that the exocyclic methylene group in the twist-brendane derivative (**35**) exerts negligible effect on the sign and shape of the circular dichroism curve due to n–π* transition and this seems also to hold in the bisnoradamantane derivatives **20** and **21**.

Turning to the optical rotatory power of 2-oxa-twist-brendane (**7**) and 2-oxabrendane (**8**), we notice that 2-oxa-twist-brendane (**7**) derived from the intrinsically chiral parent compound shows lager optical rotation. Comparison within the twist-brendane series, however, shows that 2-oxa-twist-brendane (**7**) has a smaller rotation than the parent hydrocarbon, twist-brendane. The same tendency was observed by Ganter[9] when comparison was made between the optical rotatory power of twistane and that of dioxatwistane (**9**).

Experimental Section

Infrared spectral data were obtained from a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained from a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO-DIP-SL automatic polarimeter. Circular dichroism (CD) data were measured on a JASCO J-20 spectropolarimeter with CD attachment. Elemental analyses were determined by Yanagimoto CHN-Corder type I. All the melting points and the boiling points are uncorrected.

(−)-*endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (14). The levorotatory carboxylic acid **14** was prepared from the levorotatory salt of the carboxylic acid with cinchonidine by the same procedure previously reported:[3c,10a] bp 112–114 °C (6 mm); $[\alpha]^{24}D$ −112.4° (*c* 0.61, ethanol).[15]

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.47; H, 7.32.

(+)-*endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (29). The dextrorotatory carboxylic acid **29** was prepared from the salt which was obtained from the combined mother liquors: bp 112–113.5 °C (6 mm); $[\alpha]^{25}D$ +73.1° (*c* 0.65, ethanol).

Anal. Calcd for $C_8H_{10}C_2$: C, 69.54; H, 7.30. Found: C, 69.49; H, 7.34.

(−)-*endo*-2-Hydroxymethylbicyclo[2.2.1]hept-5-ene (15). A solution of 17.2 g of **14** in 150 ml of dry ether was added to a suspension of 6.9 g of lithium aluminum hydride in 200 ml of dry ether at room temperature. The mixture was then refluxed for 4 h. After cooling with ice, to the chilled reaction mixture was added a saturated aqueous ammonium chloride solution and a solid was filtered off. A filtrate was washed with water and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to give 15.1 g of **15** (97%): bp 85–87 °C (11 mm); $[\alpha]^{25}D$ −66.6° (c 0.60, ethanol).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.29; H, 9.77.

(−)-*endo*-2-Formylbicyclo[2.2.1]hept-5-ene (10). To a mixture of 96.0 g of dry pyridine and 1.4 l. of dry methylene chloride was added 60.0 g of chromium trioxide and the mixture was then stirred for 15 min at room temperature.[16] A solution of 12.2 g of (−) alcohol **15** in 10 ml of dry methylene chloride was added to the reagent and then the reaction mixture was stirred for a further 15 min at room temperature. After the organic layer was separated, the residue was rinsed with the same solvent. Combined organic solutions were washed with dilute hydrochloric acid, saturated aqueous sodium bicarbonate, and water, and dried over magnesium sulfate. After removal of the solvent, the residue was distilled to yield 8.54 g of **10** (71%): bp 97–100 °C (66 mm); $[\alpha]^{26}D$ −69.6° (*c* 1.07, ethanol); ir (film) 3020, 2720, 1715, 1335, and 720 cm^{-1}.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.84; H, 8.23.

Photocyclization of 10. A solution of 1.14 g of the (−) aldehyde **10** in 200 ml of benzene was irradiated for 12 h with a mercury lamp (SHL-100UV, Toshiba). The crude oxetane was obtained by evaporation of the benzene at reduced pressure. Sublimation gave 650 mg of the oxetane **11** (57%): mp 136–137 °C (in a sealed tube) (lit.[5g] 136–137.5 °C); $[\alpha]^{20}D$ 0° (*c* 0.90, ethanol).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.87; H, 8.22.

(−)-*endo*-2-(1-Hydroxyethyl)bicyclo[2.2.1]hept-5-ene (16). A solution of 8.54 g of (−) aldehyde **10** in 100 ml of dry ether was added at room temperature to methylmagnesium bromide which was prepared from a large excess of methyl bromide and 4.25 g of magnesium in 100 ml of dry ether. The mixture was refluxed for 2 h and then cooled with ice. Saturated aqueous ammonium chloride solution was added to the chilled mixture. The organic layer was washed with dilute hydrochloric acid, saturated aqueous sodium bicarbonate, and water, and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to yield 8.81 g of **16** (91%): bp 104–106 °C (28 mm); $[\alpha]^{27}D$ −48.3° (*c* 0.47, ethanol); ir (film) 3350, 3020, 1100, and 720 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.00; H, 10.27.

(−)-*endo*-2-Acetylbicyclo[2.2.1]hept-5-ene (17). A solution of 6.60 g of (−) alcohol **16** in 10 ml of dry methylene chloride was added to Collins' reagent which was prepared from 29.0 g of chromium trioxide, 45.0 g of dry pyridine, and 660 ml of dry methylene chloride. The reaction mixture was then stirred for 15 min at room temperature. The organic layer was separated and the residue was rinsed with the same solvent. Combined organic solutions were

worked up by the same manner described above. The solvent was evaporated and the residue was distilled to yield 5.42 g of **17** (83%): bp 83 °C (15 mm); $[\alpha]^{22}D$ −93.6° (*c* 1.23, ethanol); ir (film) 3080, 1705, 1355, 1185, 1175, and 720 cm^{-1}.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.57; H, 8.95.

(−)-2-Methyl-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (18). A solution of 5.10 g of (−) ketone **17** in 300 ml of benzene was irradiated for 51 h with a mercury lamp (SHL-100UV, Toshiba) under a nitrogen atmosphere. After evaporation of benzene, the residue was chromatographed on silica gel. Fractions eluted with pentane–ether (9:1 volume) were distilled to give 2.87 g of **18** (56%): bp 101–105 °C (80 mm); $[\alpha]^{22}D$ −12.0° (*c* 0.88, ethanol); ir (film) 1105, 980, 858, 845, and 835 cm^{-1}; NMR (CCl_4) δ 1.34 (s, 3 H), 1.47–1.65 (m, 4 H), 1.70–2.20 (m, 2 H), 2.45–2.70 (m, 2 H), and 4.37–4.46 (m, 1 H).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.44; H, 8.95.

(+)-4-Methylenetricyclo[3.3.0.0^{3,7}]octan-2-ol (19). To a solution of 6.0 g of diethylamine in 40 ml of dry benzene was added 42 ml of a 15% solution of butyllithium in hexane with ice cooling under a nitrogen atmosphere. After the reaction mixture was warmed to room temperature, a solution of 3.30 g of (−) oxetane **18** in 40 ml of dry benzene was added to the mixture. After refluxing for 32 h under a nitrogen atmosphere, it was poured onto ice and extracted with benzene. The extract was washed with saturated aqueous ammonium chloride and water, and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm activity III) and fractions eluted with pentane–ether (4:1 volume) were distilled to give 876 mg of **19** (27%): bp 104 °C (45 mm); $[\alpha]^{26}D$ +13.2° (*c* 0.60, ethanol); ir (film) 3450, 3050, 1670, 1410, 1265, 1110, 1080, 1065, 880, and 815 cm^{-1}.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.09; H, 8.94.

(−)-4-Methylenetricyclo[3.3.0.0^{3,7}]octan-2-one (20). A solution of 850 mg of (+) alcohol **19** in 2 ml of dry methylene chloride was added to Collins' reagent from 4.4 g of chromium trioxide, 6.9 g of dry pyridine, and 110 ml of dry methylene chloride. The mixture was agitated for 20 min at room temperature. After working up by the same method described above, the solvent was evaporated. The residue was chromatographed on neutral alumina (Woelm activity III) and fractions eluted with pentane were distilled to yield 531 mg of **20** (63%): bp 123 °C (65 mm); $[\alpha]^{25}D$ −36.6° (*c* 1.24, ethanol); ir (film) 3080, 1765, 1672, 1110, 880, and 835 cm^{-1}; NMR (CCl_4) δ 1.64–1.77 (m, 4 H), 2.34–2.42 (m, 1 H), 2.45–2.57 (m, 1 H), 2.65–2.75 (m, 1 H), 2.80–2.90 (m, 1 H), 4.53 (s, 1 H), and 4.67 (s, 1 H); uv max (isooctane) 292 nm sh (ε 383), 298 sh (410), 300.5 (445), 306.5 sh (367); CD (*c* 1.87 × 10^{-2}, isooctane) [θ] (nm) +4.3 × 10^4 (190), +9.8 × 10^4 (199.5), 0 (224), 0 (245), −1.79 × 10^4 (301), −1.65 × 10^4 sh (307), 0 (335).

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.83; H, 7.57.

(−)-*endo*-2-(1-Hydroxy-2-methylpropyl)bicyclo[2.2.1]hept-5-ene (22). A solution of 6.70 g of (−) aldehyde **10** in 60 ml of dry ether was added to isopropylmagnesium bromide which was prepared from 12.3 g of isopropyl bromide and 2.43 g of magnesium in 40 ml of dry ether. The reaction mixture was gently refluxed for 4 h. To the chilled mixture was added saturated aqueous ammonium chloride solution and the inorganic solid was filtered off. The filtrate was washed with water and dried over magnesium sulfate. Removal of the solvent gave a solid, which was washed with cold hexane to yield 5.29 g of **22** (58%): mp 85–87 °C; $[\alpha]^{20}D$ −31.6° (*c* 0.47, ethanol); ir (KBr) 3330, 3050, 1390, 1370, 1000, and 720 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.19; H, 10.84.

(−)-*endo*-2-(1-Oxo-2-methylpropyl)bicyclo[2.2.1]hept-5-ene (23). A solution of 5.13 g of (−) alcohol **22** in 5 ml of dry methylene chloride was added to Collins' reagent from 18.5 g of chromium trioxide, 31.2 g of dry pyridine, and 460 ml of dry methylene chloride. The reaction mixture was then stirred for 20 min at room temperature. After working up as usual, the solvent was evaporated and the residue was distilled to give 4.47 g of **23** (88%): bp 111–112 °C (20 mm); $[\alpha]^{19}D$ −71.9° (*c* 0.42, ethanol); ir (film) 3080, 1705, 1380, 1355, and 720 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.23; H, 9.83.

(−)-2-Isopropyl-3-oxatetracyclo[4.2.1.0^{2,5}.0^{4,8}]nonane (24). A solution of 4.40 g of (−) ketone **23** in 600 ml of benzene was irradiated with a mercury lamp (SHL-100UV, Toshiba) for 35 h. After evaporation of the benzene, the residue was chromatographed on silica gel and fractions eluted with pentane were distilled to give 3.58 g of **24** (81%): bp 101–104 °C (20 mm); $[\alpha]^{20}D$ −5.78° (*c* 0.47, ethanol); ir (film) 1383, 1365, 1110, 990, and 910 cm^{-1}; NMR (CCl_4) δ 0.90 (d, 3 H, *J* = 7 Hz), 1.00 (d, 3 H, *J* = 7 Hz), 1.40–1.80 (m, 5 H), 1.87–2.00 (m, 1 H), 2.25–2.38 (m, 1 H), 2.52–2.70 (m, 1 H), 2.77–2.90 (m, 1 H), and 4.42–4.50 (m, 1 H).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.19; H, 9.81.

(+)-4-Isopropylidenetricyclo[3.3.0.0^{3,7}]octan-2-ol (25). A solution of 1.83 g of (−) oxetane **24** in 15 ml of dry benzene was added to lithium diethylamide which was prepared from 3.43 g of diethylamine, 25 ml of a 15% solution of butyllithium in hexane, and 23 ml of dry benzene. The reaction mixture was refluxed for 130 h under a nitrogen atmosphere. After usual working up, the solvent was evaporated and the residue was chromatographed on silica gel. Fractions eluted with pentane gave 0.45 g of **24** (24%) and succeeding fractions eluted with the same solvent afforded an alcoholic product which was distilled to yield 0.44 g of **25** (24%): bp 120–122 °C (20 mm); $[\alpha]^{17}D$ +18.3° (*c* 0.43, ethanol); ir (film) 3500, 1412, 1265, 1205, 1112, 1100, 1080, and 1065 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.44; H, 9.74.

(+)-4-Isopropylidenetricyclo[3.3.0.0^{3,7}]octan-2-one (21). A solution of 265 mg of (+) alcohol **25** in 5 ml of dry methylene chloride was added to Collins' reagent from 1.0 g of chromium trioxide, 1.6 g of dry pyridine, and 25 ml of dry methylene chloride, and the solution was stirred for 20 min at room temperature. After usual working up, the solvent was evaporated and the residue was chromatographed on silica gel. Fractions eluted with pentane–ether (1:1 volume) were distilled to yield 220 mg of **21** (84%): bp 150–155 °C (20 mm); $[\alpha]^{20}D$ +37.6° (*c* 0.61, ethanol); ir (film) 1755, 1440, 1365, 1275, 1140, 1115, and 820 cm^{-1}; NMR (CCl_4) δ 1.12–1.20 (m, 2 H), 1.5–1.6 (m, 2 H), 1.64 (s, 3 H), 1.69 (s, 3 H), 2.22–2.40 (m, 1 H), 2.63–2.75 (m, 2 H), and 2.90–3.10 (m, 1 H); uv max (isooctane) 290 nm sh (ε 521), 296 sh (607), 298 (616), 304 sh (538); CD (*c* 2.88 × 10^{-4}, isooctane) [θ] (nm) +3.26 × 10^4 (214), 0 (242), 0 (260), −1.37 × 10^4 (298.5), −1.34 × 10^4 sh (304), 0 (320).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.30; H, 8.76.

(±)-2-Acetoxy-4-methylenetricyclo[3.3.0.0^{3,7}]octane (26). A solution of 2.45 g of (±) alcohol **19** in 30 ml of pyridine was mixed with 10.0 g of acetic anhydride. After stirring for 3 h at 0–5 °C, the solution was kept overnight at room temperature and then poured onto ice. It was worked up as usual and the solvent was evaporated. The residue was distilled to give 1.94 g of **26** (60%): bp 125 °C (20 mm); ir (film) 3080, 1735, 1675, 1360, 1050, and 870 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.41; H, 8.02.

(±)-2-Acetoxytricyclo[3.3.0.0^{3,7}]octan-4-one (27). A solution of 1.94 g of (±) acetate **26** in 75 ml of chloroform was cooled to −78 °C and then treated with ozone until an intense blue color persisted. The solution was allowed to warm to room temperature and the excess ozone was purged by passing nitrogen through the solution. The reaction mixture was added to a mixture of 3.0 g of zinc dust, 5 ml of acetic acid, 125 ml of chloroform, and 500 ml of water, and the mixture was agitated for 8 h at room temperature. After the organic layer was separated and washed with saturated aqueous sodium carbonate and water, it was dried over magnesium sulfate. Evaporation of the solvent gave an oily product, which was distilled to give 0.89 g of **27** (45%): bp 150 °C (10 mm); ir (film) 1770, 1740, 1370, 1270, 1230, 1200, and 1045 cm^{-1}; NMR (CCl_4) δ 1.65–1.90 (m, 4 H), 1.97 (s, 3 H), 2.16–2.33 (m, 2 H), 2.55–2.77 (m, 2 H), and 4.54–4.65 (m, 1 H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.34; H, 6.72.

(−)-2-Oxatricyclo[4.3.0.0^{4,8}]nonane (7). A solution of 4.00 g of (−) alcohol **15** in 300 ml of benzene was irradiated with a mercury lamp (SHL-100UV, Toshiba) for 49 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel. Fractions eluted with pentane gave a solid which was sublimed to yield 850 mg of **7** (21%): mp 121–124 °C (in a sealed tube); $[\alpha]^{15}D$ −142° (*c* 0.70, ethanol); ir (Nujol) 1025, 945, 850, and 825 cm^{-1}; NMR ($CDCl_3$) δ 1.2–1.6 (m, 4 H), 1.7–1.9 (m, 1 H), 2.0–2.3 (m, 2 H), 2.43–2.58 (m, 1 H), 2.63–2.80 (m, 1 H), 3.5–3.7 (d, d, 1 H, *J* = 9, 3 Hz), 3.85–4.00 (d, d, 1 H, *J* = 9, 1.5 Hz), and 4.1–4.2 (m, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.56; H, 9.69.

(+)-*endo*-6-Methoxycarbonylbicyclo[2.2.1]heptan-2-one (30). A solution of 29 g of iodine and 112 g of potassium iodide in 340 ml of water was added to a solution of 15.0 g of (+) carboxylic acid **29** in 680 ml of 0.5 N aqueous sodium bicarbonate solution. The mixture was kept overnight at room temperature and then extracted with chloroform. The extract was washed with aqueous sodium thiosulfate, aqueous sodium bicarbonate, and water, and was dried over magnesium sulfate. Evaporation of the solvent gave 25.0 g of **31** (86%), to which 500 ml of 10% aqueous sodium hydroxide solution was added. The mixture was boiled for 1 h and then cooled with ice. After extraction with chloroform, the extract was washed with aqueous sodium thiosulfate and water, and was dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to give 4.40 g of *endo*-6-carboxybicyclo[2.2.1]heptan-2-one: bp 170–172 °C (5 mm); $[\alpha]^{13}D$ +16.2° (*c* 0.63, ethanol). The carboxylic acid was treated with a solution of diazomethane in ether by the usual manner. Distillation of the product yielded 4.40 g of **30** (24%): bp 144–146 °C (20 mm); $[\alpha]^{15}D$ +14.1° (*c* 1.15, ethanol); ir (film) 1750, 1735, 1220, 1195, and 1175 cm^{-1}.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.27.

(−)-*endo*-6-Hydroxymethylbicyclo[2.2.1]heptan-2-ol (32). A solution of 3.97 g of (+) keto ester **30** in 50 ml of dry ether was added to a suspension of 0.95 g of lithium aluminum hydride in 50 ml of dry ether, and the mixture was refluxed for 4 h. After cooling with ice, saturated aqueous ammonium chloride solution was added to the chilled mixture and inorganic solid was filtered off. The filtrate was washed with water and dried over magnesium sulfate. After removal of the solvent, the residue was distilled to give 2.51 g of **32** (75%): bp 147 °C (5 mm); $[\alpha]^{15}D$ −1.05° (*c* 0.72, ethanol); ir (film) 3300, 1120, 1045, and 1030 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.58; H, 10.05.

(−)-2-Oxatricyclo[4.2.1.$0^{4,8}$]nonane (8). A solution of 1.02 g of (−) diol **32** in 5 ml of dry pyridine was mixed with 1.36 g of *p*-toluenesulfonyl chloride at 0–5 °C. After stirring for 2 h at this temperature and keeping overnight at room temperature, the solution was poured onto ice and acidified with hydrochloric acid. After extraction with ether, the extract was washed with dilute hydrochloric acid, saturated aqueous sodium bicarbonate, and water, and was dried over magnesium sulfate. Removal of the solvent gave an oily product on which pentane was added. After an immiscible substance was discarded, the solution was concentrated to give a wax. This was sublimed at 70–80 °C (5 mm) to yield 220 mg of 8 (25%): mp 117–119 °C (in a sealed tube); $[\alpha]^{15}D$ −31.7° (*c* 1.15, ethanol); ir (Nujol) 1145, 1130, 1080, 1040, 1005, 990, 948, 888, and 800 cm^{-1}; NMR ($CDCl_3$) δ 1.0–1.5 (m, 4 H), 1.5–2.0 (m, 2 H), 2.05–2.40 (m, 2 H), 2.50–2.70 (m, 1 H), 3.65–3.90 (m, 2 H), and 4.20–4.42 (m, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.66; H, 9.65.

Registry No.—**7**, 58001-92-6; **8**, 58001-93-7; **10**, 58001-94-8; **11**, 22398-42-1; **14**, 20507-53-3; **15**, 42070-82-6; **16**, 13307-34-1; **17**, 58001-95-9; **18**, 58001-96-0; **19**, 57969-19-4; **20**, 57969-20-7; **21**, 57969-21-8; **22**, 13307-39-6; **23**, 58001-97-1; **24**, 58001-98-2; **25**, 57969-22-9; **26**, 57969-23-0; **27**, 57969-24-1; **29**, 58001-99-3; **30**, 57969-25-2; **32**, 933-91-5; *endo*-6-carboxybicyclo[2.2.1]heptan-2-one, 58002-00-9.

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Thermal Rearrangements of *trans*-1-Trimethylsiloxy-1-vinylcyclotridec-3-ene

Richard W. Thies* and Richard E. Bolesta

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

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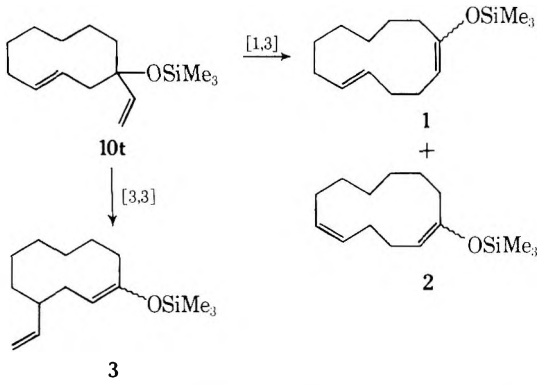
The thermal rearrangement of *trans*-1-trimethylsiloxy-1-vinylcyclotridec-3-ene (**13t**), followed by hydrolysis of the enol ethers, gives two products in comparable amounts: the [1,3] shift ring-expanded ketone, *trans*-cyclopentadec-5-en-1-one (**15t**), and the [3,3] shift product, 4-vinylcyclotridecanone (**14**). Unlike the earlier medium-sized systems, the ratio of [1,3] shift to [3,3] shift product varies with temperature. The activation parameters for the [1,3] shift compare reasonably with similar systems while those for the [3,3] shift are intermediate between the medium-sized ring cases and open-chain systems.

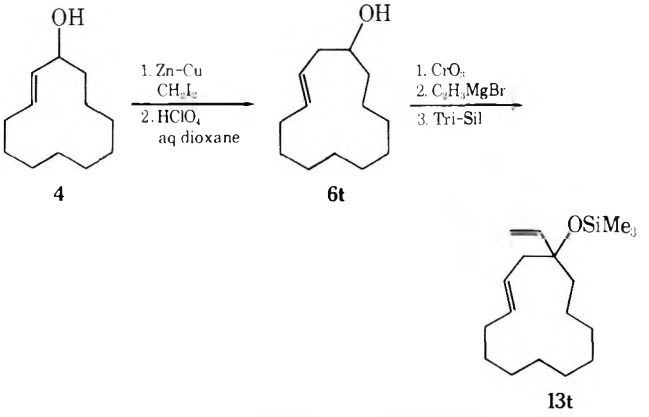
Previous papers in this series[1-3] have described the thermal rearrangements of a set of compounds exemplified by structure **10t**. The major pathway (>70%) for **10t** and for two analogues, the cis isomer, **10c**, and for the cis nine-membered-ring case, **9c**, is a [1,3] sigmatropic shift ring expansion with retention of the ring double bond stereochemistry (e.g., **1**). The [3,3] shift product (e.g., **3**) and the [1,3] shift product with double bond isomerization (e.g., **2**) are formed in minor amounts. The cis eight-membered case, **8c**, is more complex, in that the kinetically preferred pathway is a [1,3] sigmatropic shift ring contraction leading to 1-trimethylsiloxy-1,2-divinylcyclohexane which can then



interconvert with the ten-membered ring products that are analogous to **1** and **2**. The present work was carried out to determine whether the same type of two-carbon ring expansion is feasible for large ring systems. Such systems have less ring strain to be released which could result in a higher activation energy which in turn could allow other side reactions to compete.[3]

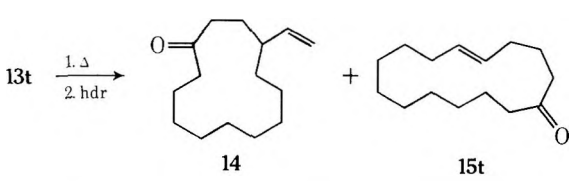
Results

Preparation of *trans*-1-Trimethylsiloxy-1-vinylcyclotridec-3-ene (13t). A mixture of *cis*- and *trans*-cyclododecene was converted to cyclododec-2-en-1-ol (**4**) by methods described previously.[4] Conversion of **4** to the title compound, **13t**, used the same steps as were used for the ten-membered ring analogue.[3] Only one isomer (trans by



infrared) was observable by gas–liquid chromatography (GLC) for **6t** or **13t**. Photolysis of **6t** or **13t** produced in each case another isomer with somewhat longer retention time which was assumed to be the cis isomer.

Thermolysis of 13t. Heating **13t** in evacuated sealed ampules (10 mg of **13t** per 10 ml ampule) at 246–299 °C gave a smooth conversion to a mixture of rearranged trimethylsilyl ethers which hydrolyzed to *trans*-cyclopentadec-5-en-1-one (**15t**) and 4-vinylcyclotridecanone (**14**). The



structures of **14** and **15t** were assigned from their spectral data, especially the NMR spectra which were spread apart using europium shift reagent, $Eu(fod)_3$. Decoupling experiments were then performed to show that there were two methylene groups between the vinyl moiety and the carbonyl for **14** and three methylenes between the double bond and the carbonyl for **15t**. The trans nature of the double bond is evident from the infrared spectrum (970 cm^{-1}).[5,6] Unlike all previous systems studied, the [3,3] shift

Table I. First-Order Rate of Disappearance and Product Ratio for 13t

Temp, °C[a]	14/(15 + 14)	$10^5 k$[b]	Corr coeff
246.0	72.0 ± 0.7	0.70 ± 0.05	0.977
254.1	69 ± 1.6	1.34 ± 0.08	0.984
284.4	60 ±1.5	13.3 ± 0.6	0.992
298.6	54 ± 0.4	39.0 ± 0.5	0.998
	Log A	E_a	Corr coeff
Total	13.7	44.9	0.9999
13t → 15t	15.5	50.3	0.9999
13t → 14	12.3	41.8	0.9999

[a] Determined by a platinum resistance thermometer in a $NaNO_2$–KNO_3 fused salt bath. [b] The rate constant is that obtained by a least-squares fit of seven to nine data points for each temperature. Internal GLC standard experiments indicated a material balance of 85% for the pyrolysis–hydrolysis sequence. Duplicate independent rate measurements differed by less than 10%.

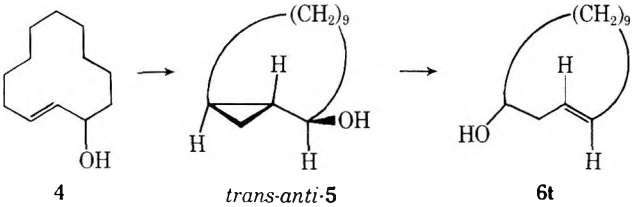
product **14t** was dominant and the ratio of **15t** to **14** was temperature dependent (Table I). That ratio did not change measurably during the time required for the kinetic measurements but the product enol ethers do slowly interconvert. This was shown by heating four samples to 90% conversion at 246 °C which gave a 72:28 ratio for **14:15t** and then heating three of the samples for times up to 19 h at 289.1 °C at which time the **14:15t** ratio was 58:42. The rate of interconversion was estimated to be about tenfold less than the rate of conversion of **13t**.

No cis isomer of **15** (**15c**) was observable under normal GLC conditions. When **15t** was reduced to the alcohol and photolyzed a second peak with somewhat longer retention time was readily observable. Oxidation back to **15** then showed **15t** and a shoulder presumed to be **15c** when optimum GLC conditions were used. Analysis of the pyrolysis samples either as the ketones or reduced to the alcohols indicated that little if any (<2%) **15c** is formed during the first 2 half-lives of reaction of **13t**. At much longer reaction times a small peak for **15c** was observed.

The rate of conversion of **13t** to **14** and **15t** was measured at four temperatures with the results shown in Table I. Good first-order behavior was observed.

Discussion

The synthesis of **13t** follows previous procedures[3,4] but the acid-catalyzed rearrangement of the cyclopropyl alcohol, **5**, is still of special interest because no large-ring or trans-fused examples have been reported. Since only the trans isomer of **6** was formed the stereochemical pattern is presumably the same as for the cis medium-sized ring systems already studied.[1-4,7,8] The Simmons–Smith reaction must be directed to give the anti isomer,[7] *trans-anti*-**5**, which then rearranges with high stereoselectivity to the trans product **6t**. We were not able to detect any cis isomer



of **4**, but if it were present it must give the *cis-anti*-**5** which would also rearrange to form **6t**.

The most prominent difference between the thermolysis of **13t** and that of the medium-sized ring analogues is that approximately half of the reaction leads to the [3,3] shift

Table II. Activation Parameters for Siloxy-Cope Rearrangements[a]

	[1,3] shift		[3,3] shift	
	E_a, kcal/mol	Log A	E_a, kcal/mol	Log A
8c	53.9	15.9	53.9	15.0
9c	47.7	14.7	47.7	13.8
10c	50.9	15.8	50.9	14.9
10t	45.1	14.2	45.1	13.3
13t	50.3	15.5	41.8	12.3

[a] Derived from earlier data assuming two competitive first-order processes.

product, **14**, whereas the medium-ring systems gave less than 15% of the [3,3] product. The small percentage formed in the medium-sized ring systems probably reflects a considerable resistance to forming either a chair or boat transition state, either of which bring the vinyl group into the crowded center of the medium-sized ring. The large ring is much more flexible so that the chair (or boat) arrangement is much more attainable. The preexponential value measured for the [3,3] shift process ($10^{12.3}$) is similar to those for other concerted Cope rearrangements (10^{10}–10^{12})[9-11] strongly suggesting a concerted path. The activation energy is considerably higher than normal (41.8 vs. 26–36 kcal/mol)[9-11] but is lower than that measured for the "boat" (44.7 kcal/mol),[9] thus suggesting a chair transition state that still encounters some resistance from the ring.

The above analysis of the [3,3] shift parameters presupposes that the [3,3] and [1,3] shift processes are competing parallel first-order reactions. The mechanistic alternative that both products arise from a common diradical cannot be rigorously excluded. The [1,3] and [3,3] activation parameters are derived from rates of product formation and thus could represent different transition states leading from the diradical to products. In principle the two competing pathways should show a small curvature in the Arrhenius plot for total disappearance of **13t**. A small curvature in the correct direction is in fact observed but the error limits are too great to be certain that the curvature is real.

It is interesting to compare **13t** with the medium-sized ring systems, **9c, 10c,** and **10t,** where the [1,3] to [3,3] product ratio was not measurably temperature dependent (see Table II). For those systems, either both [1,3] and [3,3] shift products arise from a common intermediate or the activation parameters for the two parallel pathways must fortuitously give that impression. That could only happen if the parameters for the [3,3] shift process are somewhat different for **9c, 10c,** and **10t** than for **13t;** in particular the preexponential term must be somewhat larger (ca. 10^{14} vs. 10^{12}) which generally indicates a less ordered transition state.[12] Still it is not inconceivable that the medium ring [3,3] shifts could be concerted since the chair vs. "boat" pathways for 1,5-hexadiene show a 100-fold larger preexponential term for the higher activation energy process which must still be concerted.[9]

The [1,3] shift activation parameters are similar to those observed earlier for the medium-sized ring systems. The magnitude of these activation parameters suggests a diradical; however, earlier stereochemical studies[13,14] have shown that the activation parameters for certain concerted [1,3] shifts are essentially the same as those predicted for a diradical. It has further been argued on theoretical grounds[13] that the diradical should be less favored than the concerted path even if that path is "forbidden concerted", i.e., $[_{\pi}2_s + {}_{\sigma}2_s]$.[13,15] The present results provide little evidence for or against concertedness but they do provide an estimate of the extent to which ring strain is released in the transition state regardless of mechanism. A straightforward comparison can be made with **10t** which only differs in ring size. The **13t** system has approximately 8 kcal/mol less ring strain[17] than **10t** and exhibits an activation energy which is about 5 kcal/mol greater than that for **10t.** This indicates that about 60% (⅝) of the ring strain is lost in the transition state if one assumes no ring strain in a diradical intermediate or if one assumes that the process is concerted and that the products from **13t** and **10t** have approximately the same ring strain. The latter assumption seems reasonable since saturated large rings have very little ring strain (no data is known for the unsaturated cases).

One further point of interest is the stereochemistry of the ring double bond in the ring expanded product. Retention of stereochemistry for **13t** is complete within the limits of measurement. The medium-sized ring systems, **10t, 10c, 9c,** and **8c,** exhibited loss of stereochemistry of approximately 6, 14, 14, and 35%, respectively. The heavy loss of stereochemistry for **8c** was traced to a very favorable [1,3] shift ring contraction to the six-membered ring divinyl compound which can use a facile [3,3] shift to give both cis and trans products. That process should be somewhat less favorable for **9c, 10c,** and **10t** which would contract to seven- or eight-membered divinyl compounds which would have considerably more strain than the six-membered one. Contraction of **13t** to an 11-membered-ring divinyl compound would be still less favorable, thus providing a reasonable explanation for the lack of cis product **13c.**

Experimental Section

General. Spectral measurements utilized Beckman IR-8, Varian Associates HA100, Atlas CH7, and CEC 110B instruments.[18] Analytical gas–liquid chromatography (GLC) used a Varian Aerograph Model 1200 instrument with the following columns: (A) 0.01 in. × 25 ft UCON LB 550X capillary; (B) 0.125 in. × 10 ft 10% DEGS on 60/80 Chromosorb W; (C) 0.01 in. × 50 ft DEGS PLOT[19] capillary.

***trans*-Cyclododec-2-en-1-ol (4)** was prepared in 31% yield from technical grade cyclododecene by the NBS-solvolysis method described earlier.[4] The spectra agree with those published.[6]

Bicyclo[10.1.0]tridecan-2-ol (5). A mixture of 18 g of zinc–copper couple,[20] 23 g of methylene iodide, 60 ml of anhydrous ether, and a crystal of iodine were stirred under nitrogen while heating with an oil bath at 50 °C. Once the violet color of the zinc–copper couple had formed, 20.7 g of alcohol **4** in 65 ml of anhydrous ether was added in 2 min without the reaction becoming vigorous. A second portion of methylene iodide (45 g) in 20 ml of anhydrous ether was added over 15 min. Analysis of the reaction mixture by GLC (column A, 100 °C) indicated complete reaction 8 h after final addition of methylene iodide. The flask was allowed to cool and the reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was vacuum filtered through Celite, which was then washed with ether. The ether layer was dried ($MgSO_4$) and concentrated. The product was purified by liquid chromatography on SilicAR to yield a low-melting white solid (11.5 g, 52%): ir (CCl_4) 3670, 3525, 3070, 3050, 1460, 1455, 1075, 1025, 985 cm^{-1}; NMR (CCl_4) δ 0.1–1.0 (m, 4 H), 1.0–2.3 (m, 19 H), 2.5–2.9 (m, 1 H); mass spectrum, a good analysis was not attainable because no parent peak could be found, but a P − 18 was found at the proper mass.

***trans*-Cyclotridec-3-en-1-ol (6t).** A 20.5-g sample of alcohol **5,** 150 ml of 0.12 M perchloric acid, and 585 ml of dioxane were added to a 2-l. round-bottom flask, equipped with condensor and magnetic stirrer. The solution was heated, with stirring, to 85 °C. The reaction was complete after 3 h (column A, 85 °C). The reaction solution was poured into 3 l. of 50:50 ether–pentane and 150 ml of water. The organic layer was washed once with a saturated sodium bicarbonate solution and once with saturated brine solution, and then dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue, upon cooling, was a low-melting white wax (20.5 g): ir (CCl_4) 3400, 1700, 1460, 1445, 973 cm^{-1}; NMR (CCl_4) δ 1.1–1.5 (m, 16 H), 1.6 (s, 1 H), 1.8–2.4 (m, 4 H), 3.4–3.8 (m, 1 H), 5.2–5.5 (m, 2 H); mass spectrum *m/e* 196.181 (calcd for $C_{13}H_{24}O$, *m/e* 196.183).

trans-Cyclotridec-3-en-1-one (7). A 9.49-g sample (120 mmol) of dry pyridine and 150 ml of methylene chloride were combined. To this solution was added 6.00 g (60 mmol) of chromium trioxide with stirring.[21] After 15 min, 1.96 g (10 mmol) of **6t** was added in a small amount of methylene chloride. A tarry, black deposit separated immediately. The reaction mixture was allowed to stir for an additional 15 min before 50 ml of anhydrous ether was added to coagulate the chromium salts. The mixture was gravity filtered, and the residue washed with 200 ml of anhydrous ether. The two organic phases were combined and washed three times with 100-ml portions of 5% aqueous sodium hydroxide, once with a 100-ml portion of 5% aqueous hydrochloric acid, once with a 10-ml portion of aqueous sodium bicarbonate, once with a 100-ml portion of saturated copper sulfate, and once with a 100-ml portion of saturated brine solution. The product was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated. This oil was taken on to the next reaction without further purification (crude yield 100%): ir (neat) 1710, 1460, 1455, 1360, 972 cm^{-1}; NMR (CCl_4) δ 1.0–1.9 (m, 14 H), 1.9–2.2 (m, 2 H), 2.2–2.5 (t, 2 H), 2.8–3.1 (d, 2 H), 5.3–5.6 (m, 2 H); mass spectrum *m/e* 194.167 (calcd for $C_{13}H_{22}O$, *m/e* 194.168).

trans-1-Vinylcyclotridec-3-en-1-ol (8). A 5.7-g (0.029 mol) sample of **7** was treated with vinylmagnesium bromide as described earlier[1] which gave 5.9 g (91%) of a viscous yellow oil: ir (neat) 3450, 3125, 1640, 1460, 1445, 1420, 1125, 1070, 980 cm^{-1}; NMR (CCl_4) δ 1.0–1.7 (m, 16 H), 1.7–2.1 (m, 2 H), 2.1–2.2 (d, 2 H), 2.4–2.6 (s, 1 H), 4.8–6.3 (m, 5 H); mass spectrum *m/e* 222.198 (calcd for $C_{15}H_{26}O$, *m/e* 222.198).

trans-1-Trimethylsiloxy-1-vinylcyclotridec-3-ene (13t). This compound was prepared from **8** by the procedure outlined earlier.[1] The product was vacuum transferred at 0.25 mm in an Aldrich Kugelrohr apparatus (100 °C air bath) to give **13t**: ir (CCl_4) 3110, 1455, 1415, 1225, 1055, 975, 920, 835 cm^{-1}; NMR (CCl_4) δ 0.9–1.7 (m, 16 H), 1.7–2.1 (m, 2 H), 2.1–2.3 (d, 2 H), 2.4 (s, 10 H), 4.8–6.3 (m, 5 H); mass spectrum *m/e* 294.230 (calcd for $C_{15}H_{34}OSi$, *m/e* 294.237).

Ampule Pyrolysis of *trans*-1-Trimethylsiloxy-1-vinylcyclotridec-3-ene (13t). Pyrex ampules (10 ml) were washed with acetone, water, and concentrated ammonium hydroxide, then dried overnight at 120 °C in an oven. In a typical analytical run, a 10-μl sample was added to an ampule, which was then evacuated at 0.1 mm for 30 min and sealed. The ampule was placed in an aluminum block oven maintained by a ProportionNul temperature controller or in a fused salt bath maintained by a Bailey temperature controller. The above procedure was also used with larger ampules (65 and 250 ml) using proportionately larger sample sizes. Unlike most earlier systems, higher ratios of compound to ampule size gave decreased yields. The reaction mixture was hydrolyzed as before[1] and analyzed on columns B or C. It was found that under some conditions partial hydrolysis occurred spontaneously during pyrolysis.

Structural Assignment for 4-Vinylcyclotridecanone (14). The structure was assigned by spectral properties: ir (CCl_4) 3110, 1790, 1709, 1645, 1460, 1440, 1350, 1250, 1220, 905 cm^{-1}; NMR (CCl_4) δ 1.1–1.4 (m, 14 H), 1.4–1.8 (m, 4 H), 1.8–2.2 (m, 1 H), 2.3–2.5 (m, 4 H), 4.9–5.8 (m, 3 H); mass spectrum *m/e* 222.196 (calcd for $C_{15}H_{26}O$, *m/e* (222.198). Europium shift studies combined with decoupling experiments support the assignment of the vinyl group to the 4 position.

Structural Assignment for Cyclopentadec-5-en-1-one (15t). The structure was assigned by spectral properties: ir (CCl_4) 1790, 1709, 1455, 1365, 1215, 970 cm^{-1}; NMR (CCl_4) δ 1.1–1.5 (m, 12 H), 1.5–1.8 (m, 4 H), 1.8–2.2 (m, 4 H), 2.2–2.5 (m, 4 H), 5.2–5.4 (m, 2 H); mass spectrum *m/e* 222.196 (calcd for $C_{15}H_{26}O$, *m/e* 222.198). Europium shift studies combined with decoupling experiments support the assignment of the double bond to the 5 position.

Photolysis of *trans*-Trimethylsiloxycyclotridec-3-ene (4-TMS). A solution of 100 mg of 4-TMS in 10 ml of benzene was irradiated for 1 h in a quartz tube in a Rayonet photochemical reactor. After hydrolysis as above, this produced ca. a 70:30 mixture of **4** and a slightly longer retention time component, which we presume to be the cis isomer (column A, 110 °C).

Photolysis of 13t. A solution of 10 μl of **13t** in 2 ml of benzene was irradiated for 1 h as above. This produced an 87:13 mixture of **13t** and a slightly longer retention time component which we presume to be the cis isomer (column C, 135 °C).

Photolysis of 15t. Ketone **15t** was reduced with lithium aluminum hydride to cyclopentadec-5-en-1-ol. A 20-mg sample was photolyzed in benzene for 50 min. This produced ca. an 87:13 mixture of the starting alcohol and a slightly longer retention time component which we presume to be the cis isomer (column C, 135 °C).

Kinetic Experiments. A series of 10-ml ampules were introduced into a $NaNO_2$–KNO_3 fused salt bath which was maintained by a Bailey Model 124 proportional controller. Ampules were removed at appropriate intervals and quenched in the draft of a fume hood. Each ampule was hydrolyzed and analyzed on column C. The logarithm of the ratio of the alcohol **13t** over the sum of **13t**, **14**, and **15t** was plotted vs. time and analyzed by least squares.

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Registry No.—**4**, 6221-49-4; 4-TMS, 57969-12-7; **5**, 50991-38-3; **6t**, 57969-13-8; **7**, 57969-14-9; **8**, 57969-15-0; **13t**, 57969-16-1; **14**, 57969-17-2; **15t**, 57969-18-3.

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Preparation and Substituent Effect in the Solvolysis of 1-Ethynylcyclopropyl Tosylates

J. Salaün

Laboratoire des Carbocycles, Bât, 420, Université de Paris-Sud, 91405 Orsay, France

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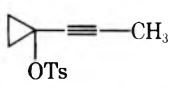
1-(1-propynyl)-, 1-(phenylethynyl)-, and 1-(cyclopropylethynyl)cyclopropyl tosylates **2, 3,** and **4** have been prepared. Their rates of reaction and the resulting products of solvolysis were determined. The relative rates (k_{rel}) in 50% ethanol (70 °C) follow: **2**, k_{rel} = 1; **3**, k_{rel} = 5.9; and **4**, k_{rel} = 133.4. The kinetic data and the product analysis are consistent with the formation of the stabilized mesomeric cation **1** as intermediate in the solvolysis reactions of 1-(cyclopropylethynyl)cyclopropyl tosylate (**4**).

Upon solvolytic conditions, simple cyclopropyl derivatives usually undergo concerted ionization and disrotatory ring opening into allyl cations.[1] Such a ring opening,[2,3] however, can be prohibited by steric[4] or conjugative interactions;[5] thus 1-cyclopropylcyclopropyl chloride[6] or tosylate[5] leads to partially unrearranged solvolysis products, i.e., 1-cyclopropylcyclopropanols.

1

In order to determine the extent to which the mesomeric cation **1** is able to prevent this ring opening by charge delocalization, we are investigating the solvolytic behavior of a variety of substituted 1-ethynylcyclopropyl tosylates; thus, depending on the electron-donating power of the substituent R, a stabilization of the positive charge of **1** can be expected. We report here our initial results with the tosylates **2, 3,** and **4** and bromide **5.**



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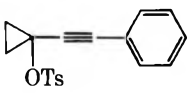

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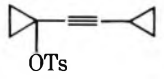

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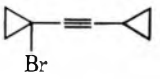
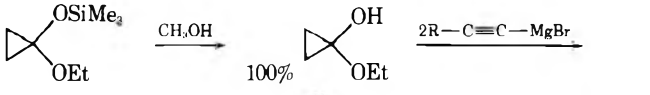
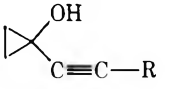


5

1-Ethoxy-1-trimethylsiloxycyclopropane (**6**), prepared from commercially available ethyl 3-chloropropanoic ester,[7] yielded on simple methanolysis the ethyl hemiketal of the cyclopropanone **7**, which provides a new and more convenient source of this known hemiketal.[8] The reaction of **7**[8] with the suitable acetylenic Grignard reagents led to the 1-alkynylcyclopropanols **8**. The tosylates **2–4** were readily prepared from the cyclopropanols **8** by usual procedures.



6 **7**



8

The bromide **5** was prepared from dicyclopropylacetylene as reported by Köbrich.[9]

The reactants **2, 3, 4,** and **5** were solvolyzed in 50% aqueous ethanol, buffered with 1.1 equiv of triethylamine in order to avoid any subsequent acid-catalyzed rearrangement of the products.[5] For each run, the products were separated by gas chromatography and their structures unequivocally proven by ir, NMR, and mass spectroscopy (or coupled mass + GC).

As shown in Table I, the products of the solvolysis are strongly dependent upon the nature of the substituent R. The tosylate **2** (R = CH_3) underwent mostly ring opening leading to the allylic alcohol **12.** On the other hand, the tosylate **3** (R = C_6H_5) gave mainly the ethyl ketone **11,** which arose from the well-known homoketonization of cyclopropanols under the conditions used.[3] The tosylate **4** (R = cyclopropyl) is more reactive and underwent very fast the total solvolytic reactions. Direct examination of the NMR spectrum of the crude material shows 81% of the unrearranged alcohol **9** and only 6% of the allylic alcohol **12.** On heating to 100 °C or on gas chromatography it is evident that the ethyl ketone **11** arises exclusively from **9.** There is also a dependency on leaving group: it would seem that the ring opening is less prohibited from the bromide **5,** which yielded 28% of allylic derivatives **11** and **12,** than from the 1-(cyclopropylethynyl)cyclopropyl tosylate **4,** which yielded only 6% of rearranged product.

The solvolysis rates of the tosylates and bromide **2–5,** measured by automatic continuous titration, are given in Table II. They increase with the increasing electron-releasing ability of the substituent R: the tosylate **3** (R = C_6H_5) reacted 5.9 times faster than **2** (R = CH_3). Strongly marked is the stabilization of the electron deficiency by the cyclopropyl group; **4** reacted 133.4 times faster than **2.**

Discussion

Although a carbon–carbon double bond stabilizes an adjacent electron deficiency by allylic resonance, it has been shown that a triple bond is highly destabilizing by a factor greater than 10^3.[10,11]

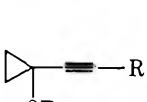
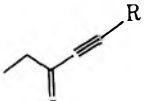
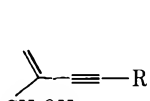
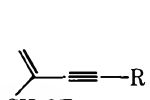
On the other hand, the solvolysis rate data on the cyclopropyl tosylates **14, 15,** and **16,**[5] shown in Table II, evidence the very large accelerating effect of an *adjacent* cyclopropyl group compared to an isopropyl group or even an allyl group.

14, R = *i*-Pr
15, R = vinyl
16, R = cyclopropyl

The data in Table II show clearly the stabilizing effect of the "substituted triple bond" in the solvolytic transition state. The higher reactivity of the tosylate **4** compared to **2** and **3** reflects in this case the superior efficiency of the cyclopropyl group, particularly relative to the phenyl group,[12] in the stabilization of the electron deficiency.

The generation of the vinyl cations **17, 18,** and **19** from

Table I. Solvolysis Products (%) of 1-Ethynylcyclopropyl Tosylates 2, 3, and 4 and Bromide 5 Buffered with 1.1 Equiv of Triethylamine in 50% Aqueous Ethanol

Compd	Temp, °C	Reaction time, h	 9	 10	 11	 12	 13	Unknown
2 R = CH_3	100	72				90		10[a]
3 R = C_6H_5	100	72	8	21	62	7	2	
4	60	2	81	9		6		4
R = 	100	0.5		9	81	6		4
5 R = 	100	72	4	39	20	21	7	7[b]

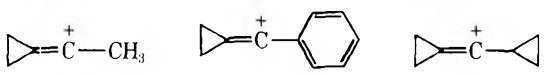
[a] As dimer of 12 from GC + mass spectra. [b] As starting bromide.

Table II. Solvolysis Rates of the Substituted 1-Ethynylcyclopropyl Tosylates and Bromide 2–5 in Aqueous Ethanol

Compd	Solvent[a]	Temp, °C	$k \times 10^4$, s^{-1} [b]	Rel rate 50E, 70 °C	m
2	50E	70.0 ± 0.1	0.141 ± 0.007	1.0	
	50E	75.0	0.230 ± 0.002		
3	50E	70.0	0.838 ± 0.017	5.94	0.60
	50E	75.0	1.320 ± 0.006		
	80E	70.0	0.090 ± 0.003		
4	50E	50.0	2.860 ± 0.015		
	50E	70.0	18.810 ± 0.015	133.40	0.64
	80E	70.0	1.797 ± 0.019		
5	50E	70.0	0.107 ± 0.001		
14[c]	50E	70.0	0.183	1.0	
15[c]	50E	70.0	1.883	10.3	
16[c]	50E	70.0	2 915	15 929	0.77

[a] 50E refers to 50% aqueous ethanol, v/v before mixing. [b] The errors reported were determined by means of a least-squares computer program. [c] From ref 5. At 70 °C, for 2 E_a = 23.38 kcal/mol; for 3, E_a = 21.69 kcal/mol; for 4, E_a = 20.87 kcal/mol.

the solvolytic reaction of the corresponding 1-bromomethylenecyclopropanes was recently reported by Hanack et al.[13]



17 18 19

The solvolysis products are dependent upon the substituent in the 1 position of the (bromomethylene)cyclopropane: while **17** rearranges almost completely with formation of the cyclobutane derivatives, **18** and **19** yield mostly the nonrearranged cyclopropyl ketones. The relative solvolysis rates (k_{rel}) for the formation of **17** in 80% aqueous ethanol at 100 °C follow: k_{rel} = 1; for **18** k_{rel} = 2.5; and for **19** k_{rel} = 100.

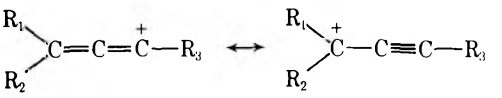
The similarity of the effect of substituents in the generation of the vinyl cations **17–19** and in the generation of the intermediate ion derived from the tosylates **2–4** (comparison of the results shown in Tables I and II with Hanack's data) would seem to suggest the occurrence of the mesomeric cation **1** in the solvolytic reactions of 1-ethynylcyclopropyl derivatives.

Indeed, the stabilization by an adjacent cyclopropyl group of the vinyl cations **19** and **20** appears clearly of the same order: they both give mostly the nonrearranged derivatives and the rate ratio k cyclopropyl/k methyl is 100 and 133.4, respectively.

20

This hypothesis seems to be confirmed by two other findings: the solvent effect and the leaving group effect.

As expected the tosylate **4** solvolyzes faster in solvents of higher ionization strength; e.g., at 70 °C, **4** reacted 10.5 times faster in 50% aqueous ethanol than in 80% ethanol corresponding to a Winstein–Grünwald m value of 0.64. For the mesomeric cation **21** obtained by Schiavelli et al. from triarylhaloallene solvolysis in aqueous acetone at 26 °C an m value of 0.69, highly comparable, was reported;[14a] while for the solvolysis of the cyclopropyl tosylate itself in aqueous ethanol at 25 °C the reported m value is only 0.50.[15]



21

A comparison of the rates of solvolysis of the tosylate **4** and bromide **5** yields a leaving group effect k_{OTs}/k_{Br} = 176; although a direct comparison is not available, it is interesting to note that an element effect k_{Br}/k_{Cl} = 56 was reported for mesomeric cations such as **21**.[14b]

Furthermore, the extensive electronic delocalization of mesomeric cations **21** has been recently determined by Olah[16] from ^{13}C NMR chemical shifts; when $R_1 = R_2 = CH_3$ and $R_3 = C_6H_5$ the results indicate that the charge localization at the allenyl end (which is a secondary benzylic vinyl cation) is equal to that of the propargyl end (tertiary carbenium center). It has been noted, however, that the charge distributions are not reflected in the subsequent reactions of such ions, since the nucleophilic attack by the solvent occurs exclusively at the propargylic position.[14,16]

In the mesomeric cation **20**, the allenyl cation form is a secondary vinyl cation with an adjacent cyclopropane ring;

it is well established that such carbenium centers are specially favored.[17] Moreover, if, as suggested, methylenecyclopropane and cyclopropyl cation ring strain effects are comparable,[18] then the relative contribution of the allenyl cation form must be important too in **20**. The lack of carbonyl absorption in the ir and of vinylic proton absorption in the NMR spectra of the crude solvolytic products would seem to indicate that the propargylic position is also relatively more reactive in the mesomeric cation **20**. This is understandable if one considers the expected delocalization of the charge at the allenyl end by the adjacent cyclopropane ring.[17]

In conclusion, from all these data, it seems reasonable to consider that the stability of the cation formed from 1-(cyclopropylethynyl)cyclopropyl tosylate **4** solvolysis should be derived chiefly from the delocalization of positive charge over the three-carbon system (see **20**), thereby allowing further delocalization into the two adjacent cyclopropane rings.

Experimental Section

Synthesis of 1-Ethoxycyclopropanol (7). A solution of 17.4 g (0.1 mol) of 1-ethoxy-1-trimethylsiloxycyclopropane[7] in 150 ml of CH_3OH was stirred at room temperature for 8 h. The solvent was removed slowly at room temperature on a rotary evaporator and a short-path distillation yielded 9.5 g (93%) of the pure 1-ethoxycyclopropanol (7): bp 59 °C (17 mm) [lit.[8] bp 60–62 °C (20 mm)]; the NMR spectrum was identical with those reported.[19]

1-(1-Propynyl)cyclopropanol (8a, R = CH_3). To 10.9 g (8.15 × 10^{-2} mol) of ethylmagnesium bromide in 100 ml of tetrahydrofuran was added slowly, at 0 °C with stirring, propyne following the known procedure.[20] To propynylmagnesium bromide (8.15 × 10^{-2} mol) was added with stirring at 0 °C 4.15 g (4.08 × 10^{-2} mol) of the hemiketal **7**. The mixture was stirred at room temperature for 3 h and heated under reflux for 2 h. The cold mixture was hydrolyzed and extracted with ether. The organic layer was dried over magnesium sulfate and concentrated to yield a light yellow oil. Distillation at reduced pressure gave 2.95 g (75%) of 1-(1-propynyl)cyclopropanol (**8a**): bp 26–27 °C (0.07 mm); ir (neat) 3090 (ν_{C-H} cyclopropane) and 2240 cm^{-1} ($\nu_{C\equiv C}$); NMR (CCl_4) δ 0.90 (m, 4 H), 1.80 (s, 3 H), 3.90 ppm (s, 1 H); MS M^+ *m/e* (rel intensity) 96 (68), 95 (31), 81 (14), 67 (100), 55 (29).

1-(Phenylethynyl)cyclopropanol (8b, R = C_6H_5). The cyclopropanol **8b** can be prepared analogously to **8a** by the reaction of phenylacetylene magnesium bromide[21] with the hemiketal **7**. After the usual work-up the cyclopropanol **8b** was obtained in 86% yield (liquid): bp 97.5 °C (0.035 mm); ir (neat) 3080 (ν_{C-H}) and 2215 cm^{-1} ($\nu_{C\equiv C}$); NMR (CCl_4) δ 1.10 (m, 4 H), 3.90 (m, 1 H), and 7.25 ppm (m, 5 H); MS M^+ *m/e* (rel intensity) 158 (53), 157 (12), 129 (100), 115 (24), 102 (21), 78 (22), 75 (22), 55 (25).

Synthesis of 1-(Cyclopropylethynyl)cyclopropanol (8c, R = Cyclopropyl). Cyclopropylacetylene. To a stirred mixture of 50 g (0.45 mol) of potassium *tert*-butoxide and 110 g of dimethyl sulfoxide, a solution of 33 g (0.22 mol) of 1-cyclopropyl-1,1-dichloroethane[22] and 20 ml of dimethyl sulfoxide was added at such a rate to maintain the temperature below 40 °C. Then the mixture was stirred at room temperature for 2 h under nitrogen. A Claisen was adapted to the flask immersed in an oil bath at 110 °C and the distillate collected to 80 °C. A careful distillation of the crude material through a spinning band column yielded 6.8 g (94%) of cyclopropylacetylene: bp 52 °C (760 mm) (lit.[23] bp 51.5–52.5 °C); ir (neat) ν_{C-H} 3080 and $\nu_{C\equiv C}$ 2110 cm^{-1}; NMR (CCl_4) δ 0.75 (m, 4 H), 1.30 (m, 1 H), and 1.58–1.6 ppm (d, 1 H).

1-(Cyclopropylethynyl)cyclopropanol (8c). A solution of 8 g (0.121 mol) of cyclopropylacetylene in 15 ml of tetrahydrofuran was added to 15.85 g (0.121 mol) of ethylmagnesium bromide at room temperature with stirring and the mixture was heated to reflux for 2 h.

Then the cyclopropylacetylene magnesium bromide was treated with the hemiketal **7** analogously to the preparation of **8a**. After the usual work-up and removal of the solvent the residue was distilled to give 5.50 g (62%) of 1-(cyclopropylethynyl)cyclopropanol (**8c**): bp 38 °C (0.06 mm); ir (neat) 3090 (ν_{C-H} cyclopropane), 2235 cm^{-1} ($\nu_{C\equiv C}$); NMR (CCl_4) δ 0.55–1.00 (m, 8 H) and 1.10–1.45 ppm (m, 1 H); MS M^+ *m/e* (rel intensity) 122 (75), 93 (31), 91 (56), 79 (100).

1-(1-Propynyl)-1-tosyloxycyclopropane (2). The tosylate **2** was obtained by conventional means through the reaction of the alcohol **8a** with tosyl chloride in pyridine (dried over molecular sieves) at −10 °C. Two recrystallizations from pentane gave the pure 1-(1-propynyl)-1-tosyloxycyclopropane (**2**): mp 48.7 °C; NMR ($CDCl_3$) δ 1.10–1.50 (m, 4 H), 1.60 (s, 3 H), 2.45 (s, 3 H), and 7.30–7.95 ppm (9, 4 H).

Anal. Calcd for $C_{13}H_{14}O_3S$: C, 62.38; H, 5.64; O, 19.17; S, 12.80. Found: C, 61.98; H, 5.65; O, 19.27; S, 12.85.

1-(Phenylethynyl)-1-tosyloxycyclopropane (3). The tosylate **3** was obtained from **8b** and tosyl chloride in pyridine. Two recrystallizations from pentane gave the pure 1-(phenylethynyl)-1-tosyloxycyclopropane (**3**): mp 116.3 °C; NMR (CCl_4) δ 1.15–1.70 (m, 4 H), 2.30 (s, 3 H), and 7.10–7.90 ppm (m, 9 H).

Anal. Calcd for $C_{18}H_{16}O_3S$: C, 69.21; H, 5.16; O, 15.36; S, 10.26. Found: C, 69.33; H, 5.14; O, 15.29; S, 10.16.

1-(Cyclopropylethynyl)-1-tosyloxycyclopropane (4). The tosylate **4** was obtained from **8c** and tosyl chloride in pyridine for 10 days at 0 °C (92%). Two recrystallizations from pentane gave the pure 1-(cyclopropylethynyl)-1-tosyloxycyclopropane (**4**): mp 61.3 °C; NMR (CCl_4) δ 0.35–1.20 (m, 8 H), 1.35–1.70 (m, 1 H), 2.45 (s, 3 H), and 7.20–7.80 (q, 4 H).

Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.83; O, 17.36; S, 11.60. Found: C, 64.93; H, 5.92; O, 17.57; S, 11.21.

Description of a Typical Product Analysis. The tosylate **2** (2.50 g, 0.01 mol) was dissolved in 40 ml of EtOH–H_2O (50:50) mixture containing 1.11 g (1.1 equiv) of triethylamine as buffer. The mixture was heated in a sealed tube at 100 °C for 3 days. After cooling the tube was opened and the solvent was removed on a rotary evaporator. The residue mixed with concentrated aqueous NaCl solution was extracted with pentane three times. The pentane extract was dried over $MgSO_4$ and concentrated on a rotary evaporator. The remainder of the pentane phase was worked up by preparative gas chromatography and each product was identified by combined GC and MS analysis.

The other solvolysis reactions were run in the same way under the conditions reported in Table I.

2-Methylene-3-pentyn-1-ol (12, R = CH_3). NMR (CCl_4) δ 1.95 (s, 3 H), 3.95 (m, 2 H), 5.30 (m, 1 H), and 5.40 ppm (m, 1 H); ir (neat) ν_{O-H} 3360, $\nu_{C\equiv C}$ 2220, $\nu_{C=C}$ 1610 cm^{-1}; MS M^+ *m/e* (rel intensity) 96 (92), 95 (52), 81 (100), and 65 (81).

1-Ethoxy-1-(phenylethynyl)cyclopropane (10, R = C_6H_5). NMR (CCl_4) δ 1.00 (m, 4 H), 1.17 (t, 3 H, J = 7 Hz), 3.80 (q, 2 H, J = 7 Hz), and 7.25 ppm (m, 5 H); ir (neat) $\nu_{C\equiv C}$ 2220 cm^{-1}; MS M^+ *m/e* (rel intensity) 186 (0.6), 171 (1), 158 (11), and 129 (100).

1-Phenyl-1-pentyn-3-one[24] (11, R = C_6H_5). NMR (CCl_4) δ 1.18 (t, 3 H, J = 7.5 Hz), 2.60 (q, 2 H, J = 7.5 Hz), and 7.35 ppm (m, 5 H); ir (neat) $\nu_{C\equiv C}$ 2200 and $\nu_{C=O}$ 1670 cm^{-1}; MS M^+ *m/e* (rel intensity) 158 (90), 141 (52), 127 (100), and 115 (31).

2-Methylene-4-phenyl-2-butyn-1-ol (12, R = C_6H_5). NMR (CCl_4) δ 3.92 (m, 2 H), 5.48 (m, 2 H), and 7.20 ppm (m, 5 H); ir ν_{OH} 3420, $\nu_{C\equiv C}$ 2200 cm^{-1}; MS M^+ *m/e* (rel intensity) 158 (100), 129 (79), 128 (53), and 115 (37).

1-Ethoxy-3-methylene-4-phenyl-3-butyne (13, R = C_6H_5). NMR (CCl_4) δ 1.20 (t, 3 H, J = 7.5 Hz), 3.60 (t, 2 H, J = 7.5 Hz), 4.00 (m, 2 H), 5.50 (m, 2 H), and 7.20 ppm (m, 5 H); ir $\nu_{C\equiv C}$ 2200 cm^{-1}; MS M^+ *m/e* (rel intensity) 186 (2), 171 (10), 158 (81), and 157 (100).

1-Ethoxy-1-(cyclopropylethynyl)-1-cyclopropane (10, R = Cyclopropyl). NMR (CCl_4) δ 0.80 (m, 8 H), 1.10 (m, 1 H), 1.20 (t, 3 H), 3.65 (q, 2 H); ir $\nu_{C\equiv C}$ 2220 cm^{-1}; MS M^+ *m/e* (rel intensity) 150 (2), 135 (4), 122 (55), 107 (43), 91 (84), and 79 (100).

1-Cyclopropyl-1-pentyn-3 one (11, R = Cyclopropyl). NMR (CCl_4) δ 0.95 (m, 4 H), 1.10 (t, 3 H), 9.30 (m, 1 H), and 2.40 ppm (q, 2 H); ir (neat) ν_{C-H} 3090, $\nu_{C\equiv C}$ 2200, and $\nu_{C=O}$ 1670 cm^{-1}; MS M^+ *m/e* (rel intensity) 122 (3), 107 (3), 93 (100), and 65 (33).

4-Cyclopropyl-2-methylene-3-butyn-1-ol (12, R = Cyclopropyl). NMR (CCl_4) δ 0.80 (m, 4 H), 1.10 (m, 1 H), 3.90 (m, 2 H), 5.20 (m, 1 H), and 5.35 ppm (m, 1 H); ir (neat) ν_{OH} 3380, ν_{C-H} 3090, $\nu_{C\equiv C}$ 2210, and $\nu_{C=C}$ 1610 cm^{-1}; MS M^+ *m/e* (rel intensity) 122 (10), 121 (9), 106 (12), 91 (25), 79 (100), and 77 (53).

Kinetic Procedures. The solutions used during the kinetic runs were prepared with absolute ethanol and distilled water. The solvolysis rates were measured by means of a Combi titrator 3D (Metrohm AG CH-9100, Herisau, Switzerland).

The pH of the solution was adjusted to 7.00. About 70 ml of the solvent mixture was transferred to the reaction vessel, which was placed in a constant temperature bath adjusted to the appropriate temperature within a range of ±0.1 °C. After the stirred solution had reached thermal equilibrium, about 25 mg (~0.1 mmol) of

reactant (2–5) was added to it. The solvolysis proceeded with continual stirring. The *p*-toluenesulfonic acid (or HBr) liberated during the solvolysis was automatically neutralized with 0.1 N NaOH solution. The titre was registered automatically on a graph, and the data was gathered in such a way that the Guggenheim method[25] could be employed for calculation of the rate constants.

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Registry No.—**2**, 57951-59-4; **3**, 57951-60-7; **4**, 57951-61-8; **5**, 39225-19-9; **6**, 27374-25-0; **7**, 13837-45-1; **8a**, 57951-62-9; **8b**, 57951-63-0; **8c**, 57951-64-1; **10** (R = C_6H_5), 57951-65-2; **10** (R = cyclopropyl), 57951-66-3; **11** (R = C_6H_5), 19307-74-5; **11** (R = cyclopropyl), 57951-67-4; **12** (R = CH_3), 57951-68-5; **12** (R = C_6H_5), 57951-69-6; **12** (R = cyclopropyl), 57951-70-9; **13** (R = C_6H_5), 57951-71-0; propynyl bromide, 2003-82-9; phenylacetylene bromide, 42560-90-7; cyclopropylacetylene, 6746-94-7; 1-cyclopropyl-1,1-dichloroethane, 40459-85-6; cyclopropylacetylene bromide, 57951-72-1; tosyl chloride, 98-59-9.

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Structure–Activity Relationships in Papain–Ligand Interactions

Corwin Hansch* and Daniel F. Calef

Seaver Chemistry Laboratory, Pomona College, Claremont, California 91711

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Quantitative structure–activity relationships have been formulated for two sets of ligands ($XC_6H_4OCOCH_2NHSO_2Me$ and $XC_6H_4OCOCH_2NHCOC_6H_5$) binding to papain. The data of Williams and co-workers are analyzed to show that K_m is correlated with electron withdrawal by inductive-field effect by X and by the polarizability of X as measured by the molar refractivity of X. It is suggested that one part of the ligand interacts with a hydrophobic pocket via desolvation and that a second part binds in a polar area without desolvation.

We have been interested in developing quantitative structure–activity relationships (QSAR) for enzyme–ligand interactions. Our work,[1-4] taken with that of others,[5-9] provides convincing evidence that the use of a multiparameter approach, based on substituent constants and regression analysis, enormously extends one's ability to cast enzymic structure–activity relationships in numerical terms. Early QSAR studies with enzymes often attempted to rationalize substituent effects on enzyme–ligand interactions with the simple Hammett equation, generally by omitting those substituents which were not well fit. More recently, more comprehensive treatments have been based on electronic, steric, and hydrophobic[10] constants for substituents. However, there has been a long-standing interest in the use of polarizability of substituents to rationalize the affinity they impart to a parent molecule for interaction with a biomacromolecule. Pauling and Pressman[11] appear to be the first to have attempted the correlation of binding constants of haptens and antibodies with molar refractivity of substituents. They showed, with certain assumptions, that one could expect a linear relationship between log K and MR where K is an equilibrium binding constant and MR is defined by the Lorentz–Lorenz equation:

$$MR = \frac{n^2 - 1}{n^2 + 2}\frac{MW}{d} \quad (1)$$

In eq 1, n is the refractive index, MW the molecular weight, and d the density of a molecule. MR is an additive property of organic compounds and extensive tables of its values for substituents have been compiled.[12] While Pauling and Pressman did not obtain a high correlation between binding constants of haptens and antibodies (this was later shown to be controlled by steric effects of substituents),[13] their basic idea appears sound.

We have found two parameters (π and MR) in our studies of QSAR of enzymes for nonspecific interactions of substituents to be necessary to correlation work. A large amount of evidence has accumulated to establish the importance of hydrophobic regions in enzymes and log P or π (from octanol–water partition coefficients)[14] appear to correlate substituent interactions in these regions.[1-10]

One must also consider the "other space" which is not hydrophobic. This nonhydrophobic space must be polar in nature; hence, one would not expect desolvation of a substituent interacting with such space to play an important role in the interaction. Pauling and Pressman envisioned

Table IA. Data Used for Formulation of Equations 4–9 for $XC_6H_4OCOCH_2NHSO_2Me$

Registry no.	Substituent X	Log $1/K_m$ Obsd	Log $1/K_m$ Calcd[a]	σ	π	MR	$\mathcal{R}$-4	$\mathcal{F}$-3,4
39092-90-7	4-OH	2.05	1.888	−0.37	−0.67	0.28	−0.64	0.29
26322-96-3	4-OMe	2.13	2.194	−0.27	−0.02	0.79	−0.51	0.26
36092-92-9	4-Me	2.08	2.110	−0.17	0.56	0.56	−0.13	−0.04
36092-93-0	3-Me	2.23	2.147	−0.07	0.56	0.56	0.00	−0.04
36092-94-1	H	1.79	1.930	0.00	0.00	0.10	0.00	0.00
36092-95-2	4-F	1.95	1.946	0.06	0.14	0.09	−0.34	0.43
36092-96-3	3-OMe	2.29	2.339	0.12	−0.02	0.79	0.00	0.26
36092-97-4	4-CHO	2.33	2.397	0.42	−0.65	0.69	0.13	0.31
36124-81-9	4-Cl	2.38	2.279	0.23	0.71	0.60	−0.15	0.41
36124-82-0	3-F	1.98	2.050	0.34	0.14	0.09	0.00	0.43
36124-83-1	4-COMe	2.57	2.654	0.50	−0.55	1.12	0.20	0.32
36124-84-2	3-NO_2	2.53	2.531	0.71	−0.28	0.74	0.00	0.67
35960-92-0	4-NO_2	2.71	2.556	0.78	−0.28	0.74	0.16	0.67

[a] Calculated via eq 7.

Table IB. Data Used for Formulation of Equations 10–14 for $XC_6H_4OCOCH_2NHCOC_6H_5$

Registry no.	Substituent X	Log $1/K_m$ Obsd	Log $1/K_m$ Calcd[a]	σ	MR	π
30022-13-0	4-NH_2	3.58	3.559	−0.66	0.54	−1.23
29736-20-7	4-Me	4.02	3.931	−0.17	0.56	0.56
2979-54-6	H	3.77	3.700	0.00	0.10	0.00
2979-52-4	4-Cl	4.00	4.253	0.23	0.60	0.71
29736-22-9	4-F	3.69	3.736	0.06	0.09	0.14
2979-53-5	3-NO_2	4.74	4.710	0.71	0.74	−0.28
3101-11-9	4-NO_2	4.85	4.761	0.78	0.74	−0.28

[a] Calculated via eq 13.

dispersion forces playing the main role in the binding of substituents to antibodies and based their thinking on the London equation.

Franks[15] has recently summarized evidence for two types of "hydrophobic bonding". In addition to the traditional type in which desolvation of an aqueous shell is the driving force, there is considerable evidence to show that two solvated groups surrounded by their flickering clusters of water molecules may be held together in solution by mutual stabilization of their water "clathrates".

The view of Franks seems to us to be the best model to explain the efficacy of MR in correlating certain types of enzyme–ligand interactions. The thought is of course similar to that of Pauling and Pressman's except that a layer of water molecules separates ligand and enzyme. In searching for examples of data to support our hypothesis, one runs into the problem that collinearity between π and MR is often so high for a given data set that either vector will correlate the data. There are also inbetween cases where collinearity is high but one variable is significantly better so that one is led to suspect certain space as being predominantly hydrophobic or polar.[4,16–18] Of course, no region of significant size in or on an enzyme would be purely hydrophobic or purely polar; we are speaking of the predominant character.

While Franks speaks of a second kind of hydrophobic interaction, we prefer to regard a hydrophobic effect as being primarily determined by desolvation of substituent and enzyme and think of a second type of nonspecific interaction which does not involve significant desolvation. The nature of this type of interaction is not clear but appears to be well modeled by MR, not π.

An example of the characterization of nonhydrophobic space can be given using the work of Loontiens et al.[19] These authors measured the binding constants between Concanavalin A and 19 4-X-phenyl-β-D-glucosides. Their results have been correlated by the following two equations[20]

	n	r	s	
Log $M_{50} = 0.097\pi + 2.37$	19	0.664	0.095	(2)
Log $M_{50} = 0.019$MR + 2.23	19	0.950	0.038	(3)

in which n represents the number of data points, r the correlation coefficient, and s the standard deviation from the regression. Although there is considerable collinearity between π and MR ($r^2 = 0.50$), MR is obviously the much more important variable. Equation 3 is highly significant ($F_{1,17} = 172$; $F_{1,17\,\alpha.001} = 15.7$); MR has been scaled by 0.1 in this equation to make it more equiscalar with π.

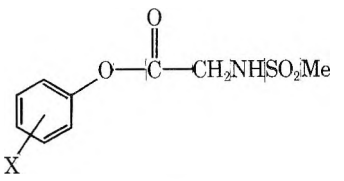
The studies of Williams[21,22] on the hydrolase papain have recently come to our attention. Williams and his coworkers have measured K_m and k_o of three sets of congeners reacting with papain. There is little variation in k_o so that hydrolysis of aryl esters by this enzyme depends mostly on K_m. An analysis of Williams' data shows that K_m correlates well with MR of the substituents and not with π.

Method

In formulating QSAR for the papain hydrolysis of the various esters, we have studied the following parameters: π, MR, σ, and σ^-. The values of these have been taken from our recent compilation.[12] As usual, we have scaled MR by 0.1. We have formulated eq 4–16 from the data in Tables I and II.

Results

The largest set of data for the papain hydrolysis studies is that for congeners of type 1. Williams[22] measured k_o/K_m for 14 derivatives and found that all but four points gave a good linear relationship with σ. The 4-$OCH_2C_6H_5$ deriva-



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tive was so insoluble that K_m values were not reported for this compound; hence we have derived eq 4–8 for 13 data points.

	n	r	s	
Log $1/K_m$ = 0.54(±0.34)σ + 2.14(±0.13)	13	0.730	0.192	(4)
Log $1/K_m$ = −0.16(±0.38)π + 2.23(±0.17)	13	0.271	0.271	(5)
Log $1/K_m$ = 0.69(±0.33)MR + 1.85(±0.21)	13	0.813	0.164	(6)
Log $1/K_m$ = 0.53(±0.23)MR + 0.37(±0.20)σ + 1.88(±0.13)	13	0.935	0.105	(7)
Log $1/K_m$ = −0.04(±0.30)π + 0.53(±0.37)σ + 2.14(±0.14)	13	0.732	0.201	(8)

Using all of the data, it is clear that MR is a more important variable than σ and that it is much more important than π. It is evident from Table IIB that π, σ, and MR are remarkably orthogonal. Therefore, we can say with some confidence that the space into which the substituents bind is not typically hydrophobic and that desolvation appears not to be involved in binding of enzyme and substrate. Equation 7 is a significant improvement over eq 6 ($F_{1,10}$ = 15; $F_{1,10\,\alpha.005}$ = 12.8). Hence, two properties of substituents are seen to promote binding: polarizability and electron-withdrawing power. The use of σ^- in place of σ in eq 7 results in a slightly poorer correlation (r = 0.922).

More insight into the nature of the electronic effect can be obtained by factoring σ into inductive and resonance components. Taft and his colleagues have discussed the importance of this operation for obtaining deeper insight into reaction mechanisms.[23] Swain and Lupton's $\mathcal{F}$ and $\mathcal{R}$ parameters[12] for inductive and resonance have been used since Taft's σ_I and σ_R set lacks values for OH and CHO groups. Because the contributions of $\mathcal{F}$ and $\mathcal{R}$ are position dependent, we first formulated an equation by the linear combination of the five terms: $\mathcal{F}$-3, $\mathcal{R}$-3, $\mathcal{F}$-4, $\mathcal{R}$-4, MR. This is of course too many terms for 13 data points; however, it was clear from this equation that $\mathcal{R}$-3 was unimportant and that the coefficients with $\mathcal{F}$-3 and $\mathcal{F}$-4 were close enough in value to be combined. This leads to eq 9

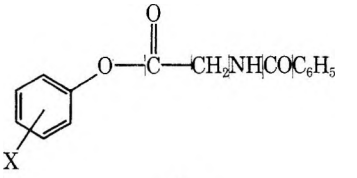
	n	r	s	
Log $1/K_m$ = 0.56(±0.22)MR + 0.51(±0.28)$\mathcal{F}$-3,4 + 0.23(±0.27)$\mathcal{R}$-4 + 1.79(±0.16)	13	0.949	0.098	(9)

which brings out the fact that the inductive-field effect and the polarizability of substituents determine K_m. While $\mathcal{R}$-4 is significant ($F_{1,9}$ = 3.5; $F_{1,9\,\alpha.1}$ = 3.4), it is of marginal importance (note confidence limits). The correlation using variables mentioned above has a standard deviation of 0.102 compared to 0.098 of eq 9.

Equations 10–14

	n	r	s	
Log $1/K_m$ = 0.90(±0.53)σ + 3.97(±0.25)	7	0.892	0.251	(10)
Log $1/K_m$ = 0.03(±0.90)π + 4.09(±0.54)	7	0.038	0.554	(11)
Log $1/K_m$ = 1.31(±1.5)MR + 3.46(±0.82)	7	0.708	0.392	(12)
Log $1/K_m$ = 0.77(±0.67)MR + 0.73(±0.37)σ + 3.62(±0.34)	7	0.971	0.148	(13)
Log $1/K_m$ = −0.17(±0.45)π + 0.96(±0.58)σ + 3.95(±0.28)	7	0.916	0.248	(14)

correlate K_m values for the hydrolysis of congeners of type 2 by papain. In this smaller set of congeners, σ appears to



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be slightly more important than MR; however, eq 13 is a significant improvement over eq 10 ($F_{1,4}$ = 9.1; $F_{1,4\alpha.05}$ = 7.7). π is of no importance. From the squared correlation matrix of Table IIB, π and MR are seen to be noncollinear. Equations 7 and 13 are in agreement with respect to π, MR, and σ. Taken alone, one cannot place much weight on eq 13 since only seven data points are correlated by two variables but, together with eq 7, a convincing case is made for a nonhydrophobic interaction of X.

A third set of congeners of the type $C_6H_5CONHCH_2COOR$ was also studied with papain.[21] However, suitable σ constants are not available for this mixed set and an analysis could not be made.

Williams correlated his data using k_o/K_m and, since k_o is essentially constant, this definition of activity produces a similar result. Equation 15 shows the relationship.

	n	r	s	
Log k_o/K_m = 0.60(±0.24)MR + 0.31(±0.20)σ + 2.95(±0.14)	13	0.930	0.110	(15)

It is again found that MR is a more important variable than σ (r for the linear relationship between log k_o/K_m and σ is 0.661, while for MR, r is 0.847). The dual-parameter equation gives an improved correlation ($F_{1,10}$ = 3.5); however, the improvement is not as great as with log $1/K_m$, indicating that electronic effects tend to cancel in the binding and hydrolysis steps.

Equations 7 and 13 can be combined by means of an indicator variable (I) which in eq 16

	n	r	s	
Log $1/K_m$ = 0.57(±0.26)MR + 0.56(±0.19)σ − 1.92(±0.15)I + 3.74(±0.17)	20	0.990	0.148	(16)

takes the value of 1 for congeners having the $NHCOC_6H_5$ moiety and zero for congeners with the $NHSO_2Me$ group; hence, the intercept of eq 16 should be the same as eq 13, which is the case within the confidence limits. One should not attach much importance to the very high correlation coefficient since this is partly the result of adding a large amount of variance by combining two data sets rather far apart in data space. The coefficients in eq 16 are close to those of eq 7 and of course within the confidence limits of those of eq 13. Equation 16 indicates the parallel QSAR for the two data sets and establishes the distance between the lines as 1.92 log $1/K_m$ units.

Table IIA. Squared Correlation Matrix for Variables Considered in Equations 4–7

	σ	π	MR	$\mathcal{F}$-3,4	$\mathcal{R}$-4
σ	1.00	0.08	0.13	0.52	0.58
π		1.00	0.06	0.14	0.00
MR			1.00	0.03	0.13
$\mathcal{F}$-3,4				1.00	0.01
$\mathcal{R}$-4					1.00

Table IIB. Squared Correlation Matrix for Variables Considered in Equations 10–14

	σ	π	MR
σ	1.00	0.07	0.17
π		1.00	0.02
MR			1.00

Discussion

Williams and his colleagues clearly showed that there is a correlation between K_m and σ in the hydrolysis of esters by papain. However, to do so it was necessary to omit a number of data points from consideration. We have advanced their efforts by showing that if the polarizability of the substituents is also considered, all data points can be correlated in a single equation. By factoring σ into resonance and inductive components it is possible to show that it is the inductive-field effect of substituents which is important in papain hydrolysis. Williams et al.[24] observed that a "lipophilic" force was also involved; by lipophilic they meant "a blanket term to cover donor–acceptor (or charge-transfer) hydrophobic and van der Waals–London dispersion forces". Our results clarify and quantify this nonspecific interaction and suggest that the classical hydrophobic interaction heavily dependent on desolvation is absent.

The role of the electronic effect of substituents is small and only the inductive-field effect is involved. It may be that electron withdrawal from the aromatic ring simply results in better van der Waals–London type interactions. Electron withdrawal could also facilitate binding of the thiol by the carbonyl group.

There is considerable knowledge of the structure of papain from both x-ray studies[25] and ligand–enzyme interactions.[26–28] Figure 1 suggests schematically how ligands of types 1 and 2 might bind to papain.

In formulating Figure 1, we have found the representation of papain by Dickerson based on the coordinates of Drenth to be most helpful.[29] The polar regions where the substituents are shown to be binding is a bank, open on one side to solvent, made up of the following nonhydrophobic amino acids: Lys 17, Asn 18, Glu 19, Gly 20, Ser 21, Gly 23, Gly 62, Asp 64, Gly 65. The pocket in which Y is depicted as interacting is made up largely of hydrophobic residues. There are two types of Y: $NHSO_2Me$ and $NHCOC_6H_5$.

Equation 16 shows that $NHCOC_6H_5$ produces 1.92 higher log $1/K_m$ than $NHSO_2Me$. Is this reasonable for the hydrophobic interaction suggested in Figure 1? The π values for these substituents are 0.49 and −1.18, respectively. The differences in hydrophobicity between the two groups is 1.67. What kind of coefficient with π would one expect for hydrophobic binding? In the case of substrates and ligands binding to the hydrophobic pocket in chymotrypsin, an average coefficient for π with eight sets of data was found to be 1.2. Assuming papain to be similar to chymotrypsin, we could expect an increase of 2.0 (i.e., 1.2 × 1.67) in log $1/K_m$. This agrees quite well with 1.92 found.

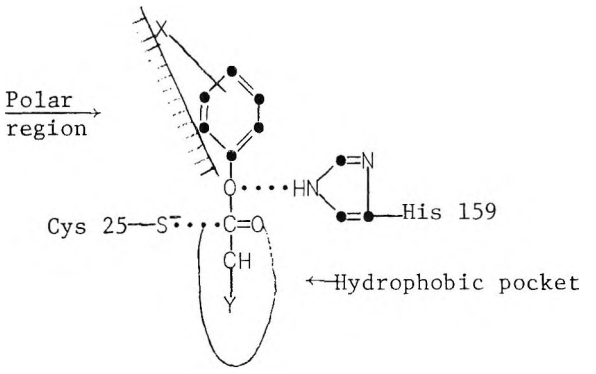

Figure 1.

We think that the model for substrate binding with papain accounts well for a variety of data now available and constitutes a basis for further study in the mapping of the papain active site.

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Registry No.—Papain, 9001-73-4.

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Interaction of a Phenylpyrazolidine Urethane with Meerwein's Salt

Sándor Barcza, Marcel K. Eberle,* Nancy Engstrom, and Gerard G. Kahle

Department of Chemistry, Division of Sandoz, Inc., East Hanover, New Jersey 07936

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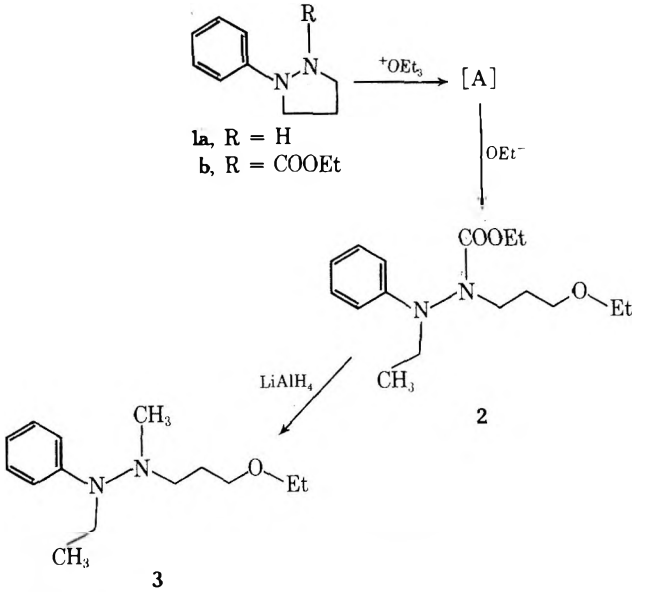
Reaction of 1-carbethoxy-2-phenylpyrazolidine with Meerwein's salt followed by neutralization with ethoxide gave 1-carbethoxy-1-(3-ethoxypropyl)-2-ethyl-2-phenylhydrazine. This product was independently synthesized from 1-ethylphenylhydrazine.

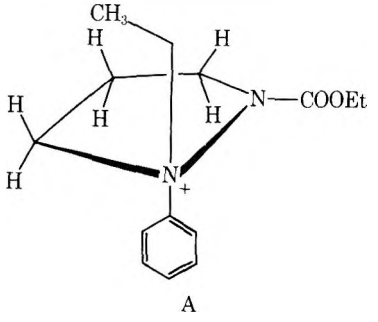
In our studies of 1-phenylpyrazolidine[1] we were interested in the course of ethylation of the carbethoxy derivative of **1a**. Treatment of **1b** with Meerwein salt[2] followed by sodium ethoxide gave a compound containing NEt, OEt, and COOEt groups (from ^{1}H NMR data) and was assigned ring-opened structure **2**. Reduction with $LiAlH_4$ gave the *N*-methyl compound **3**. Structures **2** and **3** were consistent



with ^{1}H NMR and ^{13}C NMR data (see paragraph at end of paper regarding supplementary material). The latter allowed positive identification of the site of ethylation and also revealed the course of the ring opening upon treatment with ethoxide (see Table I).

For confirmation, the urethane **2** was synthesized independently by reaction of the known 1-ethylphenylhydrazine[3] with 3-ethoxypropionyl chloride to give the corresponding hydrazide which was reduced with $LiAlH_4$ to the 1-ethyl-2-(3-ethoxypropyl)-1-phenylhydrazine. This was converted to **2** upon reaction with ethyl chloroformate and found to be identical with an authentic sample by comparison of GLC and thin film spectra.

From these results it may be concluded that the attack of the triethyloxonium fluoroborate on **1b** occurred on the nitrogen attached to the phenyl ring to yield the quaternary ammonium salt A. The addition of base resulted in an S$_N$2



A

Table I. ^{13}C NMR Shifts and Multiplicities Observed for Compounds (ppm[a])

Assignment	1b	2	3	3 (sford)[b]	
NCOO[c]	156.7[c]	Not observed[c]			
N-C$_{arom}$	150.4	148.9	149.7	s	free rotation
m-C$_{arom}$	128.9	129.5	129.0	d	
p-C$_{arom}$	121.6	119.2	117.0	d	
o-C$_{arom}$	115.6	112.9	112.5	d	
C–CH_2OEt		68.9	69.2	t	
$COCH_2CH_3$		66.6	66.4	t	
$NCOOCH_2CH_3$	62.3	62.1			
CH_3NCH_2			53.0	t	
$CH_2NCOOEt$	54.6	48.6[d]			
CH_3NCH_2			40.2	q	
$PhNCH_2CH_2$	45.4				
$PhNCH_2CH_3$		48.0[d]	36.4	t	
C–CH_2C	25.5	29.5	28.2	t	
$CH_3CH_2OCH_2$		15.4	15.3	q	
NCH_3CH_3		14.8	14.7	q	
$COOCH_2CH_3$	14.8	13.5			

[a] Data converted using $\delta_C^{CS_2}$ 193.0 ppm from Me_4Si. [b] Single frequency off-resonance decoupling. [c] The ^{13}C NMR spectrum of **2** was recorded without the presence of paramagnetic additive[4] [iron tris(pentane-2,4-dionate)]. The ^{13}C NMR spectrum of **1b** however, was recorded in the presence of the decontrasting agent and the carbonyl carbon gave rise to a distinguished peak. [d] Interchangeable.

type ring opening rather than in an E2 elimination reaction since no protons in periplanar position are readily available for ring opening with formation of a double bond.

Experimental Section

Proton NMR (^{1}H NMR) spectra were recorded on either a Varian A-60 or T-60 spectrometer and are recorded in δ values (parts per million) from Me_4Si as internal standard. The ^{13}C NMR spectra were measured on a Bruker HX-90 spectrometer and are recorded in parts per million values from Me_4Si (data converted using $\delta_C^{CS_2}$ 193.0 ppm from Me_4Si). Ir spectra were taken on a Perkin-Elmer Model 257 or 457. Gas–liquid chromatography was carried out on a Hewlett-Packard 5750 chromatograph. Mass spectra were taken on a LKB 9000 mass spectrometer. Ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, Model 14.

1-Carbethoxy-2-phenylpyrazolidine (1b). To the ice-cold mixture of 36.8 g (0.20 mol) of phenylpyrazolidine[1a] hydrochloride (**1a**), 500 ml of ether, and 250 ml of 2 N NaOH solution there was slowly added 21.6 g (0.20 mol) of ethyl chloroformate. After 20 min the organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were washed with water and dried over K_2CO_3. The solvent was evaporated to yield 41.4 g (94%) of crude **1b** which was distilled (bp 120–140 °C, 0.6 mm) to give 38.6 g (88%) of pure **1b**: ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3, J = 7 Hz, CH_3), 1.97 (quintet, 2, J = 7 Hz, $CH_2CH_2CH_2$), 3.53 (t, 2, J = 7 Hz, NCH_2CH_2), 3.65 (t, 2, J = 7 Hz, NCH_2CH_2), 4.21 (q, 2, J = 7 Hz, OCH_2CH_3), 6.7–7.5 (m, 5, C_6H_5); ^{13}C NMR (see Table I); ir (film) 1700 (C=O) 1600 cm^{-1} (aromatic); uv 237 nm (ϵ 10 600) 278 (1060). Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.26): C, 65.4; H, 7.3; N, 12.7. Found: C, 65.1; H, 7.4; N, 12.8.

1-Carbethoxy-1-(3-ethoxypropyl)-2-ethyl-2-phenylhydrazine (2). From 34.5 g of boron trifluoride etherate and 16.5 g of epi-

chlorohydrin there was prepared 31.5 g (0.17 mol) of Meerwein salt[2] following the published procedure. The salt was dissolved in 100 ml of dry methylene chloride. A solution of 33.9 g (0.15 mol) of **1b** in 50 ml of methylene chloride was added and the mixture was kept at room temperature overnight. This was poured on a solution prepared from 3.8 g (0.17 mol) of sodium in 200 ml of absolute ethanol. The mixture was stirred at room temperature for 4 h. The solvent was evaporated and the residue was extracted with ether, washed with water, and dried over K_2CO_3. After evaporation of the solvent 28.2 g (62%) of a liquid was obtained which was distilled (bp 110–130 °C, 0.13 mm) to yield 27.8 g (61%) of **2**: *m/e* 294 (M^+); ^1H NMR ($CDCl_3$) δ 0.9–1.5 (m, 9, 3 CH_3), 1.6–2.2 (m, 2, CH_2), 3.1–3.8 (m, 8, 4 CH_2), 4.10 (q, 2, J = 7 Hz, OCH_2CH_3), 6.5–7.4 (m, 5, C_6H_5); ^1H NMR ($CDCl_3$ + CCl_4 + shift reagent at 60 °C) δ 0.90 (t, 3, J = 7 Hz, NCH_2CH_3), 1.45 and 1.57 (t, 3, J = 7 Hz, 2 OCH_2CH_3), 2.0–3.0 (broad, 2, $NCH_2CH_2CH_2$), 3.20 (q, 2, J = 7 Hz, NCH_2CH_3), 3.40 (t, 2, J = 6 Hz, CH_2CH_2OEt), 4.07 (q, 2, J = 7 Hz, $CH_2OCH_2CH_3$), 5.3–6.0 (broad, 2, $COOCH_2CH_3$), 6.4–6.9 (m, 2, NCH_2CH_2); ^{13}C NMR (see Table I); ir (film) 1710 (COOEt), 1608 cm^{-1} (aromatic). Anal. Calcd for $C_{16}H_{26}N_2O_3$ (294.38): C, 65.3; H, 8.9; N, 9.5. Found: C, 65.3; H, 9.2; N, 9.7.

1-(3-Ethoxypropyl)-2-ethyl-1-methyl-2-phenylhydrazine (3). To the suspension of 1.5 g (0.04 mol) of lithium aluminum hydride in 100 ml of dry ether, a solution of 7.0 g (0.024 mol) of **2** was added dropwise. The mixture was heated to reflux for 3 h and then worked up following the usual procedures to give 4.6 g (82%) of **3**: GLC one component, a sample was distilled in a Kugelrohr; *m/e* 236 (M^+); ^1H NMR ($CDCl_3$) δ 1.17 (t, 3, J = 7 Hz, CH_2CH_3), 1.22 (t, 3, J = 7 Hz, CH_2CH_3), 1.72 (quintet, 2, J = 6.5 Hz, $CH_2CH_2CH_2$), 2.45 (s, 3, NCH_3), 2.77 (t, 2, J = 6.5 Hz, NCH_2CH_2), 3.30 (q, 2, J = 7 Hz, NCH_2CH_3), 3.46 (q, 2, J = 7 Hz, OCH_2CH_3), 3.48 (t, 2, J = 6.5 Hz, OCH_2CH_2), 6.5–7.4 (m, 5, C_6H_5); ^{13}C NMR (see Table I); ir (film) 1598 cm^{-1} (aromatic). Anal. Calcd for $C_{14}H_{24}N_2O$ (236.35): C, 71.1; H, 10.2; N, 11.9. Found: C, 71.4; H, 10.5; N, 11.8.

1-Ethyl-2-(3-ethoxypropionyl)-1-phenylhydrazide. This compound was prepared from 7.2 g (0.042 mol) of 1-ethylphenylhydrazine[3] hydrochloride and 6.8 g (0.05 mol) of 3-ethoxypropionyl chloride in the presence of 150 ml of 2 N NaOH solution following the usual procedures to give 7.1 g (72%) of product: ^1H NMR ($CDCl_3$) δ 1.0–1.4 (m, 6, 2 CH_3), 2.4–2.8 (m, 2, $OCH_2CH_2C{=}O$), 3.3–3.9 (m, 6, 3 CH_2), 6.7–7.5 (m, 5, C_6H_5), 7.9 (broad, 1, NH); ir (film) 3250 (NH), 1675 cm^{-1} (NC=O).

1-Ethyl-2-(3-ethoxypropyl)-1-phenylhydrazine. To the suspension of 1.5 g (0.04 mol) of $LiAlH_4$ in 100 ml of dry THF the solution of 5.0 g (0.02 mol) of the above hydrazide was added slowly. The mixture was heated to reflux overnight. The mixture was worked up the usual way to give 3.8 g (85%) of the product as a liquid: *m/e* 222 (M^+); ir (film) 3250 cm^{-1} (NH). This sample was contaminated with approximately 10% starting material (GLC).

1-Carbethoxy-1-(3-ethoxypropyl)-2-ethyl-2-phenylhydrazine (2). A sample (1.0 g, 0.004 mol) of the above product in 30 ml of ether was treated with 0.7 g (0.006 mol) of ethyl chloroformate in the presence of 4 ml of 2 N NaOH solution. The mixture was stirred at room temperature overnight and then worked up the usual way. The liquid was distilled two times to give 0.8 g (60%) of **2**: bp 80–90 °C (0.07 mm); GLC one component, identical with a sample of **2** prepared via **1b** (coinjection); ir (film) identical in every respect with that of **2**.

Registry No.—**1a**, 35267-14-2; **1b**, 58074-51-4; **2**, 58074-52-5; **3**, 58074-53-6; ethyl chloroformate, 54-41-3; Meerwein salt, 368-39-8; 1-ethyl-2-(3-ethoxypropionyl)-1-phenylhydrazide, 58074-54-7; 1-ethyl-1-phenylhydrazine hydrochloride, 58074-55-8; 3-ethoxypropionyl chloride, 49775-37-3; 1-ethyl-2-(3-ethoxypropyl)-1-phenylhydrazine, 58074-56-9.

Supplementary Material Available. A discussion of the NMR spectral data (2 pages). Ordering information is given on any current masthead page.

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Novel Pyridazine Formation in the Base-Catalyzed Reaction of *trans*-1,2-Dibenzoyl-3,3-diphenylcyclopropane with Hydrazine[1a,b]

Robert M. White*[1c] and Merle A. Battiste

Department of Chemistry, University of Florida, Gainesville, Florida 32611

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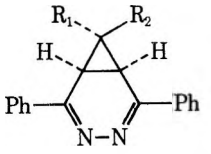
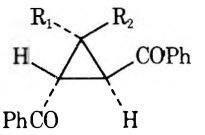
The synthesis of *exo*-2,5,7-triphenyl-3,4-diazabicyclo[4.1.0]hepta-2,4-diene (1) from *trans*-1,2-dibenzoyl-3-phenylcyclopropane (**2a**) has been accomplished in good yield by adding sodium hydroxide to a mixture of **2a** and hydrazine in ethanol. An attempt at producing 2,5,7,7-tetraphenyl-3,4-diazabicyclo[4.1.0]hepta-2,4-diene (**4**) from *trans*-1,2-dibenzoyl-3,3-diphenylcyclopropane (**3a**) by an analogous reaction produced only 3,6-diphenyl-4-benzhydrylpyridazine (**5**). It was the purpose of this study to investigate the mechanistic pathway followed in the formation of **5** and to elucidate the reasons for preferred production of **5** from **3a**. The desired heterocyclic **4** was synthesized by addition of either phenylmagnesium bromide or diphenylcadmium to 6,6-diphenyl-3-oxabicyclo[3.1.0]hexane-2,4-dione (**6**) to form 4,6,6-triphenyl-3-oxabicyclo[3.1.0]hexan-2-on-4-ol (**7**), which, on treatment with hydrazine, gave 5,7,7-triphenyl-3,4-diazabicyclo[4.1.0]hept-4-en-2-one (**8**), which, on treatment with phenyllithium, gave **4**. The heterocyclic **4** gave **5** on heating under acidic, but not basic, conditions, thus ruling out the presence of **4** during the production of **5** from **3a**. A mechanistic scheme involving 1,4,4-triphenyl-3-benzoylbut-2-en-1-one (**12**) and/or 1,4,4-triphenyl-3-benzoylbut-3-en-1-one (**13**) is presented. It is concluded that diazanorcaradiene formation from *trans*-1,2-diacylcyclopropanes under base catalysis is synthetically feasible only in cases where the *cis*-diacylcyclopropanes are sterically accessible and/or the anionic ring opening process is energetically unfavorable.

In their investigation of *exo*-2,5,7-triphenyl-3,4-diazabicyclo[4.1.0]hepta-2,4-diene (diazanorcaradiene, **1**), Amiet and Johns[2] reported that **1** could be synthesized in only low yields (7%) from *trans*-1,2-dibenzoyl-3-phenylcyclopropane (**2a**) by heating **2a** with hydrazine in ethanol for extended periods of time, whereas the cis isomer **2b** reacted rapidly and quantitatively at room temperature. In our laboratory, **1** was produced in satisfactory yield (55%) from **2a** and hydrazine in ethanol at room temperature, if sodium hydroxide was added to the mixture.[3] In view of the ready availability of *trans*-1,2-dibenzoylcyclopropane derivatives, the alkaline base–hydrazine treatment appeared to offer a

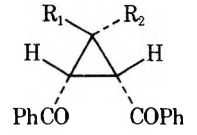
convenient and direct synthetic route to 2,5-diphenyldiazanorcaradienes.



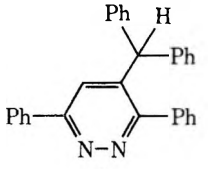
1, R_1 = Ph; R_2 = H
4, R_1 = R_2 = Ph



2a, R_1 = Ph; R_2 = H
3a, R_1 = R_2 = Ph



2b, R_1 = Ph; R_2 = H
3b, R_1 = R_2 = Ph



5

The present report describes an interesting aberrant to the pathway expected when the above hydrazine–base method is applied to the preparation of 2,5,7,7-tetraphenyl-3,4-diazabicyclo[4.1.0]hepta-2,4-diene (**4**) from the known *trans* - 1,2 - dibenzoyl - 3,3 - diphenylcyclopropane (**3a**).[4] As **4** was required for other mechanistic studies,[5] its synthesis was subsequently accomplished by a more laborious, but unambiguous four-step sequence reported herein.

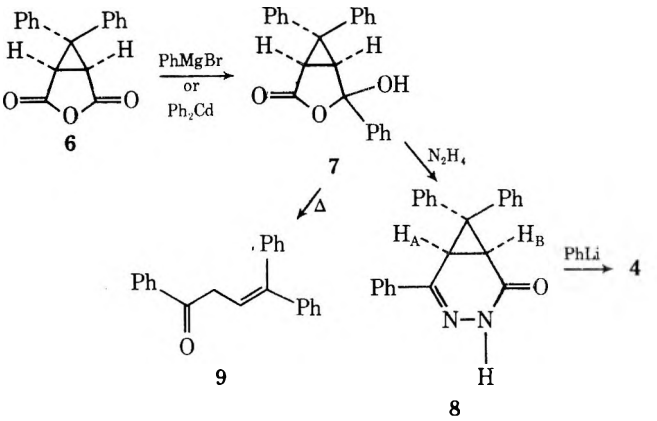
At room temperature, a stirred solution of **3**, hydrazine, and sodium hydroxide in ethanol gave no indication of the formation of the desired compound **4** as revealed by the absence of the yellow color characteristic of the 2,5-diphenyldiazanorcaradiene system. On refluxing, the reaction mixture developed an encouraging yellow color that disappeared completely after a total of 72 h. That the colorless crystals isolated from the reaction mixture were not the desired **4**, but rather an isomer **5**, was clearly discernible from NMR, mass spectral, and elemental analysis. The colorless isomer was readily identified as 3,6-diphenyl-4-benzhydrylpyridazine by its NMR spectrum (see Experimental Section), which is discussed below, and by authentic synthesis (vide infra).

Since the C-6 phenyl in pyridazine **5** is relatively free to assume coplanarity with the pyridazine ring, the ortho protons of this phenyl ring should be strongly deshielded thus accounting for the low-field two-proton multiplet at τ 1.8–2.2. However, the C-3 phenyl is sterically crowded by the bulky benzhydryl group in the 4 position and is unable to achieve coplanarity with the pyridazine ring. The C-3 ortho protons therefore occur at approximately the same chemical shift, τ 2.4–3.2, as the other remaining three protons on the C-6 phenyl and the benzhydryl group phenyl protons. The lone pyridazine ring proton is masked by the higher field aromatic multiplet. By comparison, the NMR spectrum of 3,6-diphenylpyridazine exhibits a multiplet at τ 1.72–2.02 (4 H), a singlet at 2.10 (2 H), and a multiplet at 2.32–2.67 (6 H) accounting for, respectively, the four ortho protons on the two phenyl rings, the two pyridazine ring protons, and the remaining phenyl ring protons.[3] The slightly lower chemical shift of the benzhydrylpyridazyl proton (τ 4.31) in **5** as compared to the methine proton of triphenylmethane (τ 4.538 ± 0.028)[6] is not unexpected when one considers the greater electron-withdrawing power of pyridazyl as compared to phenyl.

The intensely yellow diazanorcaradiene **4** was prepared by the method outlined in Scheme I, which is essentially a modification of the sequence of reactions developed by Maier.[7,8]

The known anhydride **6**[4,9] was prepared in good yield (61%) from diphenyldiazomethane[10] and commercial maleic anhydride. Reaction of **6** with aluminum chloride in benzene failed to produce the desired pseudoacid **7**; however, this pseudoacid was obtained in very low yield by treatment of **6** with phenylmagnesium bromide or diphenylcadmium. Pseudoacid **7** was characterized by spectral means and by its conversion to the known 1,4,4-triphenylbut-3-en-1-one (**9**)[11] on pyrolytic decarboxylation.

Scheme I



6 **7** **8** **9**

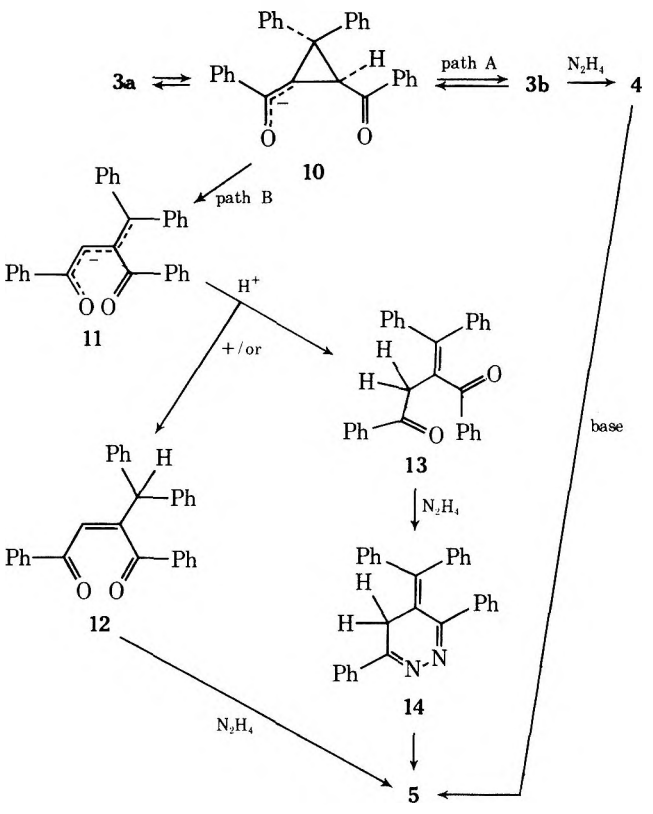
The fairly insoluble hydrazide **8** was remarkable only so far as its combustion analysis and NMR spectrum. Combustion data appeared to be consistent with the inclusion of one-half molecule of water per molecule of **8** in the crystal lattice while the NMR spectrum of **8** revealed that proton H_B (see Scheme I) was coupled not only to H_A, but also to the NH proton to the extent of 1.5 Hz. This is presumably a consequence of the "W" pattern arrangement[12] of these protons.

Treatment of **8** with phenyllithium and subsequent mild acid work-up afforded the bright yellow diazanorcaradiene **4** in moderate yield. The NMR spectrum (see Experimental Section) of **4** was consistent with two unhindered phenyls on an azine linkage (vide supra) showing multiplets at τ 1.60–2.0 (4 H, ortho protons) and 2.34–2.7 (6 H, meta and para protons). The C-7 phenyl protons appear as singlets at τ 2.71 (5 H, exo phenyl) and 3.03 (5 H, endo phenyl). The singlet at τ 6.58 (2 H) is, of course, assignable to the now magnetically indistinguishable cyclopropyl bridgehead protons. All other data for **4** were unremarkable and consistent with the assigned structure.

On refluxing in acidic dioxane, diazanorcaradiene **4** was isomerized to pyridazine **5**, thus providing an acceptable synthetic[7] verification of the structure for this pyridazine. However, **4** was unaffected (78% recovery) by the basic reaction conditions (sodium hydroxide–ethanol) utilized in the formation of **5** from **3a** and hydrazine. Thus, the mechanistic sequence depicted in Scheme II (path A) involving **4** as an intermediate (and thereby possibly accounting for the transient yellow color noted previously) in the formation of **5** is ruled out.

The most straightforward mechanistic rationalization for the formation of **5** from **3a** is that outlined in path B of Scheme II. Electrocyclic ring opening of the enolate ion **10** to give the oxapentadienyl anion **11** is expected to be an energetically favorable process. Protonation of **11** should afford either or both enediones **12** and **13**, although **13** would be favored on kinetic and thermodynamic grounds. In this regard Schecter and co-workers[13] have recently isolated an enedione analogous to **13** from mild acid work-up of the "blood-red filtrate" obtained from the treatment of *trans*-2,3-dibenzoylspiro[cyclopropane-1,9′-fluorene] (**3a**, R_1, R_2 = *o,o′*-biphenylene) with methanolic potassium hydroxide. These workers provide convincing evidence that this fluo-

Scheme II



renyl enedione is the same diketone isolated earlier by Horner and Lingnau[14] and shown to react with hydrazine hydrate to yield an "inner azine", $C_{29}H_{20}N_2$.[14] The latter workers[14] did not assign structures for either the diketone or the cyclic azine.

While in our system no separate attempt was made to isolate the diketones **12** or **13** from treatment of **3a** with base, the presence of one or the other or both may be inferred by analogy to the fluorenyl system[13,14] and by subsequent trapping with hydrazine to afford **5** either directly, in the case of **12**, or indirectly, via the cyclic azine **14**, in the case of **13**. The transient yellow color observed during the progress of the reaction is consistent with the intermediacy of the enediones and/or cyclic azine **14**.

In accord with the preceding mechanistic scheme the contrasting reactivity of the *trans*-1,2-dibenzoylcyclopropanes **2a** and **3a** toward hydrazine in basic media can now be explained on the basis of different steric and electronic requirements for base-catalyzed isomerization vs. ring opening. Thus, the additional phenyl substituent at C-3 would be expected to greatly enhance the rate of ring opening of **3a** relative to **2a** through the extra conjugation provided in the transition state. On the other hand, isomerization of **3a** to the cis diketone **3b** should be severely hampered by the increased steric crowding between cis benzoyl groups and phenyl ring. This steric problem is avoided in the monophenyl derivative **2a** by preferential isomerization to diketone **2b** in which the benzoyl groups and phenyl ring have the cis,anti configuration shown. Hence, it may be reasonably concluded that diazanorcaradiene formation from *trans*-1,2-diacylcyclopropanes under base catalysis is synthetically feasible only in cases where the *cis*-diacylcyclopropanes are sterically accessible and/or the anionic ring opening process is energetically unfavorable.

Experimental Section[15]

2,5,7-Triphenyl-3,4-diazabicyclo[4.1.0]hepta-2,4-diene (1). The stirring of 1.27 g (3.90 mmol) of *trans*-1,2-dibenzoyl-3-phenylcyclopropane (**2a**), 90 mg of sodium hydroxide, and 0.50 ml (10 mmol) of hydrazine hydrate in 500 ml of absolute ethanol for 72 h at room temperature resulted in the formation of a yellow suspended solid. Filtration followed by recrystallization from 95% ethanol yielded 687 mg (2.15 mmol, 55%) of bright yellow needles, mp 232–233 °C dec (lit.[2] 235 °C). The spectral data were in agreement with those reported.[2]

3,6-Diphenyl-4-benzhydrylpyridazine (5). A. A solution of 7.51 g (18.7 mmol) of *trans*-1,2-dibenzoyl-3,3-diphenylcyclopropane (**3a**), 1.84 ml (56.1 mmol) of anhydrous 97% hydrazine, and 0.36 g of sodium hydroxide in 700 ml of absolute ethanol was refluxed for 72 h. During reflux, the reaction mixture initially turned yellow, but at the end was totally colorless. The solid that resulted on evaporation of solvent was recrystallized first from chloroform–hexane and then from 95% ethanol to yield two crops of colorless rhombs weighing a total of 4.85 g (12.2 mmol, 65%), mp 185.7–186.0 °C.

B. A sample of 100 mg of 2,5,7,7-tetraphenyl-3,4-diazabicyclo[4.1.0]hepta-2,4-diene (**4**) was refluxed for 3 h in 50 ml of dioxane containing 0.5 ml of 37% hydrochloric acid to yield a bright yellow solution which, after neutralization, removal of solvent, and chromatography over basic alumina with chloroform, gave 46 mg (46%) of **5**. Recrystallization from ethanol gave material melting at 177.5–179 °C: NMR ($CDCl_3$) τ 1.86–2.16 (m, 2 H, aromatic), 2.4–3.23 (m, 19 H, aromatic), and 4.31 (s, 1 H, benzhydryl proton); mass spectrum (70 eV) *m/e* (rel intensity) 398 (100), 67 (13), and 65 (13); ir (KBr) 2950, 1575, 1490, 1450, 1390, 1190, 1080, 1030, 1000, 790, 765, 740, 705, and 700 cm^{-1}.

Anal. Calcd for $C_{29}H_{22}N_2$: C, 87.40; H, 5.57; N, 7.03. Found: C, 87.39; H, 5.61; N, 6.98.

6,6-Diphenyl-2,4-diketo-3-oxabicyclo[3.1.0]hexane (6). To a solution of 5.45 g (55.6 mmol) of commercial maleic anhydride in 400 ml of warm benzeneas added with magnetic stirring 11.99 g (61.75 mmol) of diphenyldiazomethane in a small amount of benzene. On mixing, immediate gas evolution and decolorization began. After stirring for 12 h, the mixture was flash evaporated and the resulting slightly pink mass was broken up, washed with low-boiling petroleum ether, and recrystallized from cyclohexane to yield 9.0 g (34 mmol, 61%, lit.[10] 25.3%) of snow-white, fine needles, mp 161.0–161.3 °C (lit.[10] 162 °C). The NMR spectrum of **6** agreed with that previously cited.[10]

4,6,6-Triphenyl-3-oxabicyclo[3.1.0]hexan-2-on-4-ol (7). A. Phenylmagnesium bromide (39.5 mmol), prepared by the standard technique in 75 ml of diethyl ether, was added over 45 min to a vigorously stirred solution of 10.4 g (39.4 mmol) of **6** in 1200 ml of dry toluene precooled to −68 to −75 °C. The reaction mixture was allowed to warm to room temperature and added to an ice–water slush containing 8.6 g (87 mmol) of 37% hydrochloric acid. Upon flash evaporation the dried toluene layer yielded a gummy mass which was crystallized by the addition of a small amount of cold benzene. The crude, brown crystals were dissolved in an aqueous solution of 8.4 g (100 mmol) of sodium bicarbonate and the resulting solution was filtered. The pseudoacid **7** was precipitated from the bicarbonate solution by acidification with 37% hydrochloric acid. The resulting solid was recrystallized from benzene to give two crops of pseudoacid weighing a total of 1.49 g (4.37 mmol of 11.1%) and melting at 197–198 and 188.5–189.5 °C (effervescence).

B. Using the standard technique, diphenylcadmium was synthesized from 9.72 g (400 mmol) of magnesium, 47.1 g (300 mmol) of bromobenzene, and 31.2 g (171 mmol) of anhydrous cadmium chloride.

The diphenylcadmium reagent was leached from its reaction mixture with two 100-ml portions of benzene, filtered, and mixed with 8.98 g (34.0 mmol) of **6** in 300 ml of benzene to yield, after standing for 36 h, a gummy precipitate to which was added 9.0 g (91 mmol) of 37% hydrochloric acid in an ice–water slush. Upon evaporation the benzene layer yielded yellow crystals which were stirred overnight with a solution of 8.4 g (100 mmol) of sodium bicarbonate. Acidification of the aqueous solution produced very little of the desired pseudoacid as the residue remaining from the bicarbonate treatment contained most of the product. The total yield after a recrystallization from benzene was 2.45 g (7.17 mmol, 21%) of the colorless, crystalline **7**: mp ca. 190 °C (effervescence); NMR ($CDCl_3$) τ 1.76–2.0 (m, 2 H, benzoyl ortho protons), 2.20–2.97 (m, 13 H, aromatic), 6.48 (AB quartet, J_{AB} = 8.0 Hz, 2 H, cyclopropyl protons), −1.4 (v br s, 1 H, COOH); mass spectrum (70 eV) *m/e* (rel intensity) 342 (1), 298 (16), 220 (23), 193 (23), 192 (13), 191 (13), 165 (10), 105 (21), 103 (100), 77 (29); ir (KBr) 2940, 2510, 1730, 1630, 1590, 1570, 1460, 1250, 1240, 955, 750, 720, 710, 695, and 690 cm^{-1}.

Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.48; H, 5.43.

1,4,4-Triphenylbut-3-en-1-one (9). A sample of 100 mg (0.292 mmol) of **7** was heated neat at about 200 °C until gas evolution ceased. The brown melt was recrystallized twice from diethyl ether–light petroleum ether to yield 14 mg (0.047 mmol, 16%) of slightly yellow needles, mp 125.0–125.7 °C (lit.[11] 126–126.5 °C). A separate sample of **7** was pyrolyzed neat in an NMR tube to give the spectrum described below.

NMR ($CDCl_3$) showed τ 2.05–2.31 (m, 2 H, benzoyl ortho protons), 2.42–3.0 (m, 13 H, aromatic), 3.59 (t, J = 7.0 Hz, 1 H, H_3), 6.21 (d, J = 7.0 Hz, 2 H, H_2); ir (KBr) 2900, 1670 (lit.[11] 1690), 1435, 1330, 1210, 995, 770, 765, 745, 700, 695, 685 cm^{-1}.

5,7,7-Triphenyl-3,4-diazabicyclo[4.1.0]hept-4-en-2-one (8). To 4.3 ml (4.3 g, 86 mmol) of hydrazine hydrate in 400 ml of absolute ethanol was added 2.47 g (7.22 mmol) of **7**. After stirring for 12 h, a precipitate appeared and was filtered off after another 24 h of stirring to yield 1.77 g (5.22 mmol, 72.3%) of colorless crystals of **8**, mp 244.0–245.0 °C. An analytical sample was obtained on recrystallization from ethanol: mp 244.7–245.2 °C; NMR ($CDCl_3$) τ 1.9 (v br s, 1 H, NH), 1.95–2.13 (m, 2 H, C-5 phenyl ortho protons), 2.40–3.16 (m, 13 H, aromatic), and 6.88 (AB quartet, J_{AB} = 8.0 Hz, 2 H, H_A and H_B) (the upfield half of the AB quartet appears as a doublet of doublets owing to further coupling with the NH proton, J_{BN} = 1.5 and J_{AN} = 0.0 Hz as determined from an HA-100 spectrum); mass spectrum (70 eV) *m/e* (rel intensity) 338 (24), 337 (16), 235 (39), 193 (22), 192 (100), 191 (28), 166 (13), 165 (47), 115 (12), and 77 (13); ir (KBr) 3100, 3000, 2850, 1670, 1495, 1445, 1365, 1320, 1070, 775, 760, 705, and 692 cm^{-1}.

Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 79.50, 79.63; H, 5.71, 5.63; N, 8.04. Calcd for $C_{23}H_{18}N_2O \cdot \frac{1}{2}H_2O$: C, 79.51; H, 5.51; 8.07.

2,5,7,7-Tetraphenyl-3,4-diazabicyclo[4.1.0]hepta-2,4-diene (4). Phenyllithium (9.94 mmol) prepared from 197 mg (28.4 mmol) of lithium and 2.23 g (14.2 mmol) of bromobenzene in 60 ml of dry diethyl ether was added dropwise to a magnetically stirred solution of 674 mg (1.99 mmol) of **8** in about 100 ml of freshly distilled tetrahydrofuran (THF). The initial transient red color that appeared as each drop of phenyllithium made contact with the THF solution remained firm after about one-fifth of the addition had been completed.

The deep red reaction mixture was stirred for an additional 30 min and then poured onto an ice–water slush containing 800 mg (13 mmol) of glacial acetic acid. The pale yellow compound was extracted with diethyl ether and chromatographed over basic alumina to yield 374 mg (0.939 mmol, 47.2%) of bright yellow, beautiful needles: mp 227.0–227.5 °C dec; NMR ($CDCl_3$) τ 1.60–2.0 (m, 4 H, ortho protons C-2 and C-5 phenyls), 2.34–2.7 (m, 6 H, meta and para protons C-2 and C-5 phenyls), 2.71 (s, 5 H, exo C-7 phenyl protons), 3.03 (s, 5 H, endo C-7 phenyl protons), and 6.58 (s, 2 H, cyclopropyl protons); mass spectrum (70 eV) *m/e* (rel intensity) 398 (40), 370 (39), 296 (25), 295 (100), 294 (23), 193 (22), 192 (18), and 166 (25); ir (KBr) 2940, 1540, 1495, 1450, 1395, 765, 755, 705, and 690 cm^{-1}.

Anal. Calcd for $C_{29}H_{22}N_2$: C, 87.40; H, 5.57; N, 7.03. Found: C, 87.44; H, 5.58; N, 6.93.

Attempted Base-Catalyzed Rearrangement of 4. A mixture of 93 mg of **4** and 19 mg of sodium hydroxide was refluxed for 75 h in 25 ml of absolute ethanol to give a still yellow, but cloudy mixture which, after filtration and chromatography over basic alumina, yielded 73 mg (78% recovery) of **4**, mp 231–231.5 °C dec. The NMR spectrum of the recovered material was identical with that of authentic **4**.

Registry No.—**3a**, 57694-77-6; **4**, 57694-78-7; **5**, 57694-79-8; **6**, 57694-80-1; **7**, 57694-81-2; **8**, 57694-82-3; **9**, 57694-83-4; hydrazine, 302-01-2; phenyl bromide, 108-86-1; diphenylcadmium, 2674-04-6; phenyllithium, 591-51-5.

References and Notes

(1) (a) Taken in part from the Ph.D. Dissertation presented by R.M.W., March 1972, to the Graduate School of the University of Florida. (b) Financial support of this research, in part, by the National Science Foundation is gratefully acknowledged. (c) Address all correspondence to this author at Clinical Chemistry, North Carolina Memorial Hospital, Chapel Hill, N.C. 27514.
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(15) All melting points were obtained using a Thomas-Hoover Unimelt apparatus and are uncorrected. Mass spectra were obtained on a Perkin-Hitachi RMU-9E instrument at 70 eV. Nuclear magnetic resonance spectra were recorded on a Varian A-60A instrument unless otherwise noted. Infrared spectra were procured on either a Perkin-Elmer Model 137 or Model 337.

Pycnolide, a *seco*-Germacradienolide from *Liatris pycnostachya*, and Other Antitumor Constituents of *Liatris* Species[1,2]

Werner Herz* and Ram P. Sharma

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

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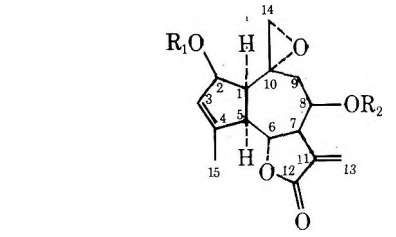
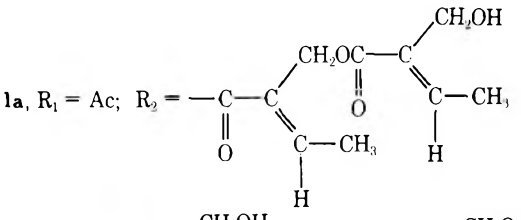
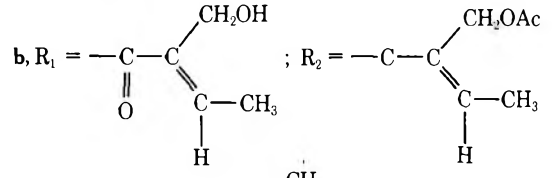
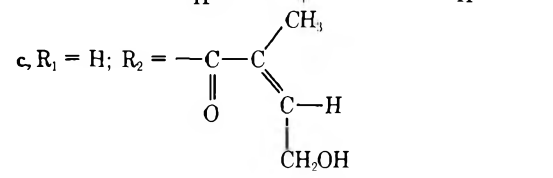
Further study of a *Liatris pycnostachya* Michx. extract yielded pycnolide (**4a**), a 2,3-seco-1(10),4,5-germacradienolide, whose structure determination by means of chemical transformations and ^1H and ^{13}C NMR spectrometry is detailed. A chlorine-containing guaianolide, spicatin hydrochloride (**3b**), was also found. The previously known cytotoxic guaianolide spicatin (**1a**), the antileukemic 5,10-epoxygermacranolide chapliatrin (**11**), and euparin (**9**) were isolated from *L. tenuifolia* Nutt. whereas *L. scabra* (Greene) K. Schum. yielded the cytotoxic heliangolide eleganin (**10**). *L. earlei* (Greene) K. Schum. and *L. pauciflora* Pursh gave small amounts of complex lactone mixtures.

In a previous article[3] we reported inter alia the isolation of the complex ester guaianolides spicatin (**1a**) and epoxyspicatin (**2a**) from the less polar fractions of a *Liatris pycnostachya* Michx. extract. Since then, spicatin, also found in *L. spicata*,[3] has been shown to be cytotoxic[5] as were graminiliatrin (**2c**) and deoxygraminiliatrin (**1c**) from *L. graminifolia*[3] and eleganin (**10**) from *L. elegans*.[6] Epoxyspicatin (**2a**) and chapliatrin (**11**, stereochemistry at C-3, C-4, and C-10 tentative)[1] from *L. chapmanii*[7] and *L. gracilis*[1] also exhibited significant in vivo activity against P388 lymphocytic anemia. In the present communication we report isolation and structure determination of spicatin hydrochloride (**3b**) and pycnolide (**4a**) from the more polar fractions of the *L. pycnostachya* extract. Pycnolide, a 2,3-

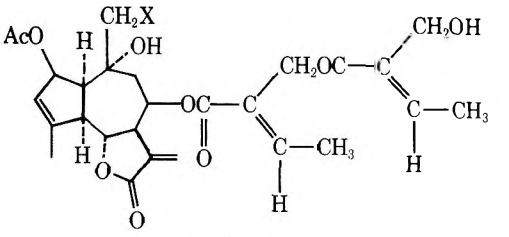








2a, R_1, R_2 as in **1a**
b, R_1, R_2 as in **1b**
c, R_1, R_2 as in **1c**



3a, X = Br
b, X = Cl

seco-1(10),4,5-germacradienolide, is the first *seco*-germacrane derivative encountered in nature. We also describe the results of our examination of *L. tenuifolia* Nutt., *L. scabra* (Greene) K. Schum., *L. pauciflora* Pursh, and *L. earlei* (Greene) K. Schum.[8]

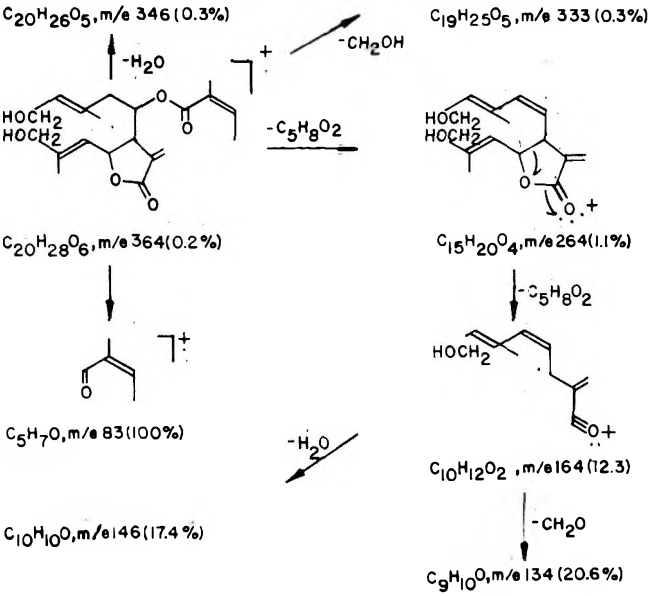
Rechromatography of the more polar fractions of the *L. pycnostachya* extract afforded first a crystalline chlorine-containing sesquiterpene $C_{27}H_{33}O_{10}Cl$ whose physical properties resembled those of spicatin hydrobromide (**3a**), a substance prepared from spicatin for x-ray analytical purposes.[4] Direct comparison with spicatin hydrochloride (**3b**), obtained by treatment of spicatin with hydrochloric acid, established identity.[9] A second, considerably more polar substance could not be induced to crystallize and was named pycnolide.

Pycnolide (**4a**), $C_{20}H_{28}O_6$ (high-resolution mass spectrum and elemental analysis), $[\alpha]^{22}D$ +39.8°, was an α-methylene γ-lactone (ir bands at 1765 and 1650 cm^{-1}, narrowly split NMR doublets at 6.36 and 5.70 ppm); two other oxygen atoms were part of a five-carbon unsaturated ester side chain (ir band at 1720 cm^{-1}) as evidenced by facile loss of a $C_5H_8O_2$ fragment on electron impact (see Scheme I) and by the appearance of an ion C_5H_7O as the base peak. The nature of this ester side chain was revealed by the NMR spectrum (Table I), which had the characteristic peaks of an angelate (vinyl multiplet at 6.1 ppm allylically coupled to a vinyl methyl at 1.83 ppm and vicinally coupled to a vinyl methyl at 1.93 ppm, the latter being long-range coupled to the first vinyl methyl resonance).

Treatment of pycnolide with acetic anhydride–pyridine resulted in formation of a diacetate (**4b**); in the NMR spectrum, this resulted in a downfield shift of two sets of signals, the first an AB system, from 4.16 to 4.54 ppm, and the second a two-proton singlet, from 4.06 to 4.52 ppm. Consequently pycnolide had two primary hydroxyl groups (ir band at 3400 cm^{-1}) and the functionality of all oxygen atoms was established.

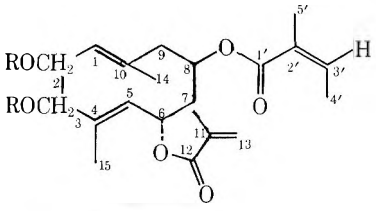
The NMR spectrum of pycnolide also displayed two somewhat broadened three-proton singlets at 1.73 and 1.83 ppm, an observation which indicated the presence of two

Scheme I. Mass Spectral Fragmentation of Pycnolide

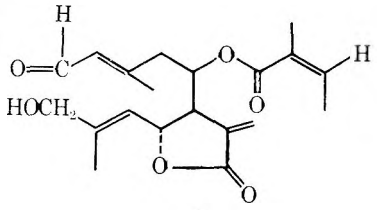


additional vinyl methyl groups. Irradiation at 5.30 ppm sharpened the resonance at 1.73 ppm and irradiation at 5.52 ppm sharpened the resonance at 1.83 ppm. Consequently pycnolide contained two $-C(CH_3)=CH-$ units, a conclusion which in conjunction with the previous deductions and the molecular formula required that pycnolide had no rings other than that of the lactone. Evidence for formula **4a** which seemed biogenetically plausible and where the numbering is that used in the supposed precursor germacradienolide was provided by spin decoupling experiments which will now be detailed.

Irradiation at the frequency of H-7 (3.10 ppm) converted the narrowly split doublets of H-13a and H-13b to singlets, collapsed a doublet of doublets at 5.35 ppm (H-6 or H-8) to a doublet (J = 9.5 Hz), and simplified a multiplet at 5.52 ppm (H-8 or H-6). Irradiation at 5.35 ppm simplified the



4a, R = H
b, R = Ac
c, R = CPh_3



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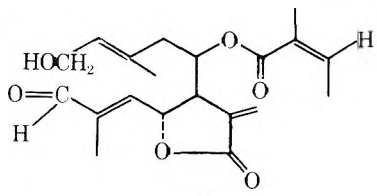
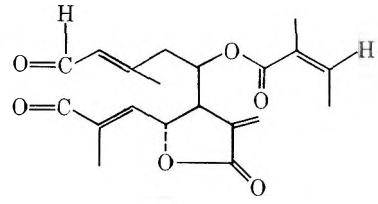
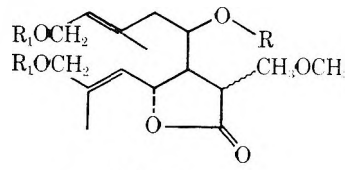


6



7



8a, R, R_1 = H
b, R = H; R_1 = Ac
c, R = H; R_1 = CPh

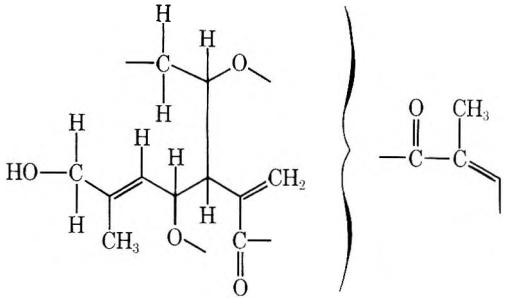
Table I. ^{1}H NMR Spectra of Pycnolide and Derivatives[a]

Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15[b]	H-3′	H-4′[b]	H-5′[b]	Misc
4a	5.30 t br (6)	4.16[c]	4.06[d]	5.52 d br (9.5)	5.35 dd (9.5, 5.3)	3.10 m (5.3, 2.8, 2.6)	5.52 m (8.5, 6)	2.45 dd (15, 8.5) 2.16 dd (15, 6)	6.30 d (2.8) 5.70 d (2.6)	1.73 br	1.83 br	6.1 m	1.93 m	1.83 br	
4b	5.34 t br (6)	4.54[c]	4.52[d]	5.48 d br (9.5)	5.26 dd (9.5, 5.3)	3.07 m	5.48 m	2.32 dd (15, 8.5) (15, 6) 2.25 dd (15, 6)	6.38 d (2.8) 5.76 d (2.6)	1.79 br	1.85 br	6.0 m	1.93 m	1.85 br	2.01[b], 2.02[b] (Ac)
4c[e]	*f*	3.60[c]	3.65[d]	*f*	*f*	3.17 m	*f*	2.39[c]	6.45 d (2.5) 5.84 d (2.2)	1.58 br	1.78 br	6.14 m	1.93 m	1.85 br	7.8[g]
5	5.80 d br (7.8)	9.94[d] (7.8)	4.10[d]	5.54 d br (10.2)	5.29 dd (10.2, 5.2)	3.1 m	5.54 m	2.55 dd (15, 8.5) 2.42 dd (15, 6)	6.39 d (2.5) 5.75 d (2.2)	2.26 br	1.82 br	6.10 m	1.92 m	1.82 br	
6	5.40 t br (6)	4.10[c]	9.50	6.30 d br (8)	5.45 dd (8, 5.1)	3.2 m	5.45	2.35 dd (15, 8.5) 2.25 dd (15, 6)	6.46 d (2.5) 5.8 t d (2.2)	1.75 br	1.85 br	6.12 m	1.97 m	1.93 br	
7	5.80 d br (7.5)	9.93[d] (7.8)	9.49	6.35 d br (8.5)	5.40 dd (8.5, 5.1)	3.2 m	5.54 m	2.46[c]	6.50 d (2.2) 5.88 d (2.2)	2.24 br	1.83 br	6.14 m	1.92 m	1.90 br	
8a	5.33 t br (7)	4.13[c]	4.02[d]	5.52 d br (9)	5.22 t (9)	2.40 m	3.92 m	2.08[c]	3.66[c]	1.65 br	1.76 br				2.88 (H-11) 3.36 (OMe)
8b	5.38 t br (7)	4.58[c]	4.52[d]	5.54 d br (9)	5.22 t (9)	2.40 m	4.02 m	2.08[c]	3.68 m	1.73 br	1.81 br				3.36 (OMe)

[a] Run at 270 MHz in $CDCl_3$ solution on a Bruker HFX-270 instrument with Me_4Si as internal standard. Values are in parts per million. Multiplicities are indicated by the usual symbols; d, doublet; t triplet; br, broadened singlet; m, multiplet whose center is given. Unmarked signals are singlets. Figures in parentheses are coupling constants in hertz. [b] Intensity three protons. [c] Center of AB system, two protons. [d] Two protons. [e] Run at 60 MHz on Varian HA-60 instrument. [f] Obscured signal. [g] Aromatic protons.

signal of H-7 as well as that of a second proton superimposed on the multiplet at 5.52 ppm which (vide supra) was coupled allylically to the vinyl methyl resonance at 1.83 ppm. Irradiation at 5.52 ppm sharpened this vinyl methyl signal and simplified the H-7 multiplet as expected, converted the doublet of doublets at 5.35 ppm to a doublet (J = 5.3 Hz), and collapsed the AB components of an ABX system at 2.45 and 2.16 ppm to sharp doublets. Hence one of the two protons in the multiplet at 5.52 ppm was adjacent to a methylene group, the other being vinylic. Since a proton under a lactone oxygen usually appears at higher field than a proton under an ester side chain, the protons in the 5.52-ppm multiplet were provisionally identified with H-5 and H-8 and the proton responsible for the 5.35-ppm signal with H-6.

Oxidation of pycnolide with MnO_2 gave two monoaldehydes **5** and **6** and the dialdehyde **7**. In the NMR spectrum of **6**, the signal of H-5, now β to an α,β-unsaturated aldehyde function, had experienced a significant downfield shift to 6.36 ppm and was clearly coupled not only to the vinyl methyl group at 1.85 ppm, but also to a doublet of doublets at 5.45 ppm (H-6) superimposed on the multiplet of H-8. In the NMR spectrum of **7**, the signals of H-6 and H-8 were distinct, a circumstance which permitted unambiguous sequencing, by spin decoupling, of the framework C-3–C-9 as in A.



A

The remaining four-carbon unit, $-C(CH_3)=CHCH_2OH$ in pycnolide and $-C(CH_3)=CHCHO$ in **5** and **7**, was clearly recognizable in the NMR spectra, the vinyl methyl signal being allylically coupled to the vinyl proton (vide supra) and experiencing a significant downfield shift, from near 1.75 to 2.25 ppm, on oxidation of the hydroxymethylene group to the aldehyde. It could be attached to A in one, and only one, way to give **4a** (devoid of stereochemistry) where the only remaining ambiguity was the orientation of the lactone ring, provisionally assumed to be closed to C-6.

This matter was settled as follows. Methanolysis of pycnolide (MeOH, NaOMe, room temperature, 10–12 h) resulted in loss of the angeloyl ester side chain and afforded a substance **8a**. In the NMR spectrum of this compound the H-8 multiplet, formerly near 5 ppm, had undergone a diamagnetic shift to 3.92 ppm. On the other hand the signal near 5.3 ppm had not been affected significantly and was still spin coupled to the H-5 vinyl proton near 5.5 ppm. Consequently the lactone rings of **8a** and of pycnolide are closed to C-6 and the ester side chain is attached to C-8.

The relatively simple fragmentation of pycnolide on electron impact (Scheme I) is fully consonant with this deduction. Initial loss of angelic acid gives rise to an ion of m/e 264 ($C_{15}H_{20}O_4$).

The next significant ion of lower mass is an ion $C_{10}H_{12}O_2$ (m/e 164) which could arise as shown in Scheme I; corresponding ions of mass 206, 162, 164, and 162, respectively, appear in the mass spectra of **4b**, **5**, **6**, and **7**. This ion further loses H_2O to give an ion of mass 146 ($C_{10}H_{10}O$) or CH_2O to give an ion of mass 134 ($C_9H_{10}O$); both ions are present in the mass spectra of **4b** and **6**, but a corresponding ion of mass 144 is absent from the mass spectra of **5** and **7**, thus confirming the proposed scheme.

Table II. ^{13}C NMR Spectrum of Pycnolide[a]

Signal no.	4a	Assignment
1	169.7	C-1′
2	166.8	C-12
3	142.7	C-10
4	138.8 d	C-3′
5	135.9	C-4
6	132.3	C-11
7	128.9 d	C-5
8	127.2	C-2′
9	123.3 t	C-13
10	121.6 d	C-1
11	74.6 d	C-6
12	71.3 d	C-8
13	66.3 t	C-3
14	58.7 t	C-2
15	47.7 d	C-7
16	41.9 t	C-9
17	20.3 q	C-14
18	15.8 q	C-15
19	15.6 q	C-4′
20	14.0 q	C-5′

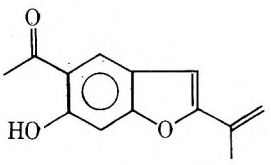
[a] Run in $CDCl_3$ on a Bruker HX-270 MHz instrument with Me_4Si as internal standard.

The ^{13}C NMR spectrum of pycnolide (Table II) is fully in accord with the proposed structure and was helpful in ruling out other possibilities prior to the work discussed in the previous paragraphs. Tentative assignments are based on predicted shifts and comparisons with data in the literature[1] and in our files.

The stereochemistry of pycnolide was established in the following manner. The pronounced paramagnetic shift of the C-10 methyl signal on going from **4a** to **5** or **7** clearly demonstrated trans, or E, stereochemistry around the 1,10 double bond.[13,14] The trans or E configuration of the 4,5 double bond was evident from the NMR spectra of **6** and **7**. The shift of the aldehyde proton on C-1 (near 9.5 ppm) is indicative of a cis relationship between the aldehyde function and the vinylic hydrogen, trans aldehydes with this substitution pattern giving rise to signals near 10 ppm or higher.[16]

The absolute configuration at C-8 was determined by Horeau's method. Initially, the primary hydroxyls of pycnolide were protected by conversion to the bis trityl ether **4c** which was converted to **8c** by methanolysis (NMR spectrum). However, attempts at purification resulted in partial cleavage of **8c** to **8a**, previously prepared more directly by methanolysis of **4a**. Selective acetylation of **8a** (acetic anhydride–pyridine, 10 min) gave the diacetate **8b** which was esterified with excess (+)-α-phenylbutyric anhydride. The recovered α-phenylbutyric acid was dextrorotatory (14.2% optical yield). Hence the configuration at C-8 is R; i.e, the ester function is β if the structure is depicted as in the formulas.

The value of $J_{6,7}$ in **4a**–**7** (~5.2, see Table I) would be appropriate for either a cis or a trans lactone ring closure (models). However, $J_{6,7}$ = 9 Hz in **8a** and **8b** indicates that the lactone ring is trans fused. Since $J_{7,13}$ < 3 Hz (see Table I), Samek's rule ($J_{7,13} \geq 3$ Hz for trans-fused lactones)[17] is therefore apparently not applicable to *seco*-germacradienolides of the type represented by pycnolide.[18] If the C-7 side chain is β (i.e., 7 R) as in all sesquiterpene lactones of established stereochemistry, the hydrogen at C-6 must be β (6R). If this be so, the observed positive Cotton effect (θ_{240} +990) is not in agreement with the empirical rule of Stöcklin et al.[19,20] Unfortunately, all compounds en-



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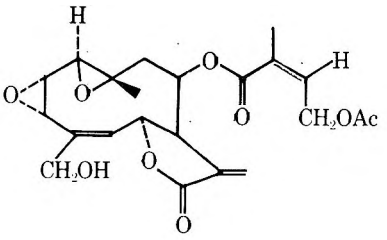

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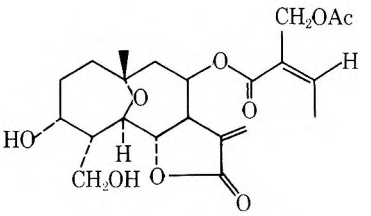

11

countered in the present work were noncrystalline; means to confirm the stereochemistry at C-6 by x-ray analysis and to relate the chirality of the lactone system of pycnolide to the Cotton effect are therefore lacking at present.[21]

Pycnolide represents a new type of sesquiterpene structure, a *seco*-germacrane, whose biogenesis obviously involves cleavage of the 2,3 bond of a germacrane precursor. However it is highly unusual for the following reason. In other seco-type structures, whether sesquiterpenoid, diterpenoid, or triterpenoid, the oxidation states of the carbon atoms at the points of scission are higher than prior to cleavage. In pycnolide, on the other hand, enzymatically induced scission must be followed by two simultaneous or consecutive reduction steps.

Examination of *Liatris tenuifolia* gave the benzofuran derivative euparin (**9**) and, as the only components of a complex lactone mixture which could be separated and identified, spicatin (**1a**) and the 5,10-epoxygermacranolide chapliatrin (**11**) previously[1] isolated from *L. chapmanii* and *L. gracilis* Pursh. *L. scabra* (Greene) K. Schum. also yielded a mixture of lactones from which the heliangolide eleganin (**10**) previously[6] found in *L. elegans* (Walt.) Michx. could be separated by extensive chromatography. Attempts to separate lactone mixtures obtained in small amount only by extraction of *L. earlei* (Greene) K. Schum. and *L. pauciflora* Pursh have so far not been successful.

Experimental Section[22]

Isolation of Spicatin Hydrochloride and Pycnolide. The extraction of *L. pycnostachya* has been described previously.[3] The $CHCl_3$ and $CHCl_3$–MeOH eluates (10:1) gave a mixture, wt 5.5 g, which was rechromatographed over 200 g of silicic acid, 200-ml fractions being collected in the following order: $CHCl_3$ (10 fr), $CHCl_3$–MeOH (99:1, 10 fr), $CHCl_3$–MeOH (49:1, 10 fr), $CHCl_3$–MeOH (99:1, 10 fr), $CHCl_3$–MeOH (9:1, 10 fr) and $CHCl_3$–MeOH (4:1, 10 fr). Fractions 5–8 yielded 0.5 g of spicatin hydrochloride (**3b**), identical with material prepared from spicatin (see below). Fractions 34–39 gave 2 g of pycnolide (**4a**) which was purified by preparative TLC on silica gel $PF_{254-355}$ ($CHCl_3$–MeOH, 8:1). The noncrystalline substance had $[\alpha]^{22}D$ +39.8° (*c* 1.1, $CHCl_3$); CD curve $[\theta]_{240}$ +990; ir bands at 3400, 1765, 1720, 1650, 1230, 960, and 850 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74; O, 26.34; mol wt, 364.1884. Found: C, 65.44; H, 7.79; O, 26.76; mol wt (MS), 364.1890.

Spicatin Hydrochloride. A solution of 0.1 g of spicatin in 40 ml of absolute ethanol and 0.01 ml of 38% hydrochloric acid was stirred overnight at room temperature and evaporated in vacuo. A solution of the gummy residue in $CHCl_3$ exhibited two main spots on TLC. Preparative TLC (silica gel, $CHCl_3$–ether–MeOH, 30:30:1) developed three times gave 40 mg of starting material and 44 mg of solid spicatin hydrochloride which was recrystallized from ethyl acetate–hexane: mp 122–123 °C dec; ir bands at 3480, 3405, 1770, 1715, and 1655 cm^{-1}, high-resolution mass spectrum peaks at *m/e* (composition, %) 552 ($C_{27}H_{33}O_{10}Cl$, M^+, 0.23), 492 ($C_{25}H_{29}O_8Cl$, 24.2), 474 ($C_{25}H_{27}O_7Cl$, 0.54), 456 ($C_{25}H_{25}O_6Cl$, 0.55), 395 ($C_{20}H_{24}O_6Cl$, 0.65), 278 ($C_{15}H_{15}O_3Cl$, 7.9), 260 ($C_{15}H_{13}O_2Cl$, 7.4), 115 ($C_5H_2O_3$, 24.1), 99 ($C_5H_7O_2$, 100), 81 (C_5H_5O, 55.6); NMR signals ($CDCl_3$, 90 MHz) at 7.06 q and 6.88 q (*J* = 7 Hz, H-3′ and H-8′), 6.24 d (3.6) and 5.48 d (3.1, H-13), 5.81 m (H-3), 5.75 m (H-8), 5.41 m (H-2), 4.87 (H-5′), 4.56 dd (10, 8, H-6), 4.30 (H-10′), 3.94 m (H-7), 3.57 m (H-14), 2.77 dd (10, 9, H-5), 2.37 m (H-9), 2.05 (Ac), 2.03 (H-15), 1.93 d and 1.89 d (7, H-4′ and H-9′).

Anal. Calcd for $C_{27}H_{33}O_{10}Cl$: Cl, 6.41. Found: Cl, 6.28.

Spicatin Hydrobromide (3a). The reaction of 0.1 g of spicatin in 40 ml of absolute ethanol with 0.01 ml of 48% HBr was carried out and worked up as described in the previous paragraph. Preparative TLC (silica gel, $CHCl_3$–ether–MeOH, 30:30:1) developed three times gave yellowish crystals of hydrobromide (wt mg) and 40 mg of starting material. Recrystallization from MeOH–H_2O gave colorless crystals: mp 95–98 °C dec; ir bands at 3485, 3410, 1770, 1715, and 1655 cm^{-1}; NMR signals ($CDCl_3$, 90 MHz) at 7.05 q and 6.87 q (*J* = 7 Hz, H-3′ and H-8′), 6.23 d (3.6) and 5.47 d (3.1, H-13), 5.81 m (H-3), 5.75 m (H-8), 5.41 m (H-2), 4.87 (H-5′), 4.56 dd (10, 8, H-6), 4.30 br (H-10′) 3.94 m (H-7), 3.52 m (H-14), 2.73 dd (10, 9, H-5), 2.42 m (H-9), 2.03 (H-15) 2.01 (Ac), 1.93 d and 1.87 d (7, H-4′ and H-9′).

Anal. Calcd for $C_{27}H_{33}O_{10}Br$: Br, 13.37. Found: Br, 12.60.

Diacetylpycnolide (4b). Reaction of 50 mg of pycnolide with 1 ml of acetic anhydride and 0.5 ml of pyridine followed by the usual work-up gave **4b** as a gum which had in bands at 1765, 1735, 1720, 1650, 1250, 960, and 850 cm^{-}.

Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19; O, 28.54; mol wt, 448.2095. Found: C, 64.10; H, 7.06; O, 27.78; mol wt (MS), 448.2121.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, %) 348 ($C_{19}H_{24}O_6$, 1.0), 306 ($C_{17}H_{22}O_5$, 1.7), 288 ($C_{17}H_{20}O4$, 2.0), 246 ($C_{15}H_{18}O_3$, 2.8), 228 ($C_{15}H_{16}O_2$, 5.3), 206 ($C_{12}H_{14}O_3$, 4.3), 178 ($C_{11}H_{14}O_2$, 1), 164 ($C_{10}H_{12}O_2$, 6.5), 146 ($C_{10}H_{10}O$, 54.3), 134 ($C_9H_{10}O$, 3.1), 83 (C_5H_7O, 100).

MnO_2 Oxidation of Pycnolide. A solution of 0.2 g of pycnolide in 10 ml of AR $CHCl_3$ was stirred with 0.5 g of active MnO_2, the reaction being monitored by TLC. After 4 h, when starting material had disappeared, the mixture was filtered and the residue thoroughly washed with $CHCl_3$. The combined filtrate and washings were evaporated; the residue was purified by preparative TLC (silica gel $PF_{254-355}$, solvent benzene–ethyl acetate, 1:1). One major and two minor products were isolated. The major product (R_f 0.4) was identified as the monoaldehyde **5**, wt 0.105 g; the minor products (R_f 0.5 and 0.6) were **6** (0.025 g) and **7** (0.020 g), respectively. Attempts to obtain **5**, **6**, and **7** in crystalline form were unsuccessful. Longer reaction time or excess MnO_2 did not give better yields of **6** and **7**, but when pure **5** or **6** was exposed to fresh MnO_2, the reaction proceeded quickly to give **7** in 100% yield. Similiar observations were recorded in the case of ligantrol.[23]

Substance **5** had ir bands at 3400, 1760, 1710, 1660, 1230, 970, and 850 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; O, 26.49; mol wt, 362.1728. Found: C, 65.27; H, 7.14; O, 26.98; mol wt (MS), 362.1726.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, %) 262 ($C_{15}H_{18}O_4$, 1.5), 244 ($C_{15}H_{16}O_3$, 1.9), 233 ($C_{14}H_{17}O_3$, 1.4), 232 ($C_{14}H_{16}O_3$, 1.4), 231 ($C_{14}H_{15}O_3$, 1.2), 162 ($C_{10}H_{10}O_2$, 5.6), 161 ($C_{10}H_9O_2$, 11.8), 134 ($C_9H_{10}O$, 5.4), 133 (C_9H_9O, 21), and 83 (C_5H_7O, 100).

Substance **6** exhibited ir bands at 3400, 1760, 1710, 1660, 1240, 980, and 850 cm^{-1}. Its low-resolution mass spectrum had significant peaks at *m/e* 362 (M^+), 344 ($M - H_2O$), 262 ($M - C_5H_8O_2$), 164 ($M - C_5H_8O_2 - C_5H_6O_2$), 146 ($M - C_5H_8O_2 - C_5H_6O_2 - H_2O$), 134 ($M - C_5H_8O_2 - C_5H_6O_2 - CH_2O$), and 83 ($C_5H_7O$, base peak).

Substance **7** had ir bands at 1760, 1710, 1660, 1240, 1050, and 850 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71; O, 26.64; mol wt, 360. Found: C, 65.80; H, 7.16; O, 26.88; mol wt (MS), 360.

Other significant peaks in the low-resolution mass spectrum were at *m/e* 331 ($M - CHO$), 260 ($M - C_5H_8O_2$), 231 ($M - C_5H_8O_2 - CHO$), 162 ($M - 2C_5H_8O_2$), 134 ($M - 2C_5H_8O_2 - CO$), 83 (C_5H_7O, base peak).

Methanolysis of Pycnolide. A solution of 0.2 g of pycnolide in 10 ml of anhydrous MeOH was stirred with 0.3 g of NaOMe under nitrogen. After 0.5 h, all starting material had disappeared (TLC).

The mixture was acidified with acetic acid, extracted with $CHCl_3$, washed, dried, and evaporated. The residue gave a single spot on TLC; the NMR spectrum indicated retention of the angeloyl ester side chain and addition of MeOH to the α,β unsaturated lactone function. Extension of the time of methanolysis to 12 h followed by the usual work-up resulted in isolation of gummy **8a** which was purified by preparative TLC (solvent $CHCl_3$–MeOH, 10:1), ir bands at 3400, 1770, 1230, 1050, and 950 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34; O, 30.53; mol wt, 314. Found: C, 60.43; H, 8.25; O, 31.19; mol wt (MS), 314.

Other significant peaks in the low-resulting mass spectrum were at *m/e* 282 (M − MeOH), 265 (M − MeOH − OH) 264 (M − MeOH − H_2O).

The gummy diacetate **8b** was prepared by allowing 0.08 g of **8a** to stand with 1 ml of acetic anhydride and 0.5 ml of pyridine for 10 min at 10 °C. The usual work-up gave 0.075 g of **8b** which was purified by preparative TLC (solvent Bz–ethyl acetate, 1:2).

Anal. Calcd for $C_{20}H_{30}O_8$: C, 60.29; H, 7.59; O, 32.12; mol wt, 398. Found: C, 60.03; H, 7.18; O, 32.31; mol wt (MS), 398.

Other significant peaks in the low-resolution mass spectrum were at *m/e* 314 (M − $2C_2H_2O$), 282 (M − $2C_2H_2O$ − MeOH), and 264 (M − $2C_2H_2O$ − MeOH − H_2O).

A solution of 0.203 g (6.55×10^{-4} mol) of (±)-α-phenylbutyric anhydride and 0.075 g of **8b** in 1 ml of pyridine was kept at room temperature for 48 h. Excess anhydride was destroyed by 2 ml of water. The solution was extracted with ethyl acetate and the extract washed thoroughly with water, 5% $NaHCO_3$ solution, and again with water. The combined aqueous layers were extracted with $CHCl_3$, acidified with 1 N H_2SO_4, and extracted again with $CHCl_3$. Evaporation of the last $CHCl_3$ extracts gave 0.140 g of pure (by TLC criteria) α-phenylbutyric anhydride, $[\alpha]^{24}D$ 2.55°. This corresponded to an optical yield of 14.2%.

Extraction of *Liatris tenuifolia*. Above-ground parts of *L. tenuifolia Nutt.* collected by R. Lazor on Sept 23, 1971, 3 miles east of the junction of U.S. route 319 and State road 155, Thomas County, Ga. (Lazor no. 5587 on deposit in herbarium of Florida State University) was extracted with $CHCl_3$ and worked up in the usual manner. The crude gum, 87 g, was chromatographed over 1.1 kg of silicic acid, 1-l. fractions being collected in the following order: benzene (15 fr), Bz–$CHCl_3$ (4:1, 15 fr), Bz–$CHCl_3$ (1:1, 15 fr), Bz–$CHCl_3$ (1:4, 15 fr), $CHCl_3$ (35 fr), $CHCl_3$–MeOH (99:1, 8 fr), $CHCl_3$–MeOH (49:1, 9 fr), and $CHCl_3$–MeOH (19:1, 9 fr). Fraction 3, wt 0.22 g, consisted of yellow crystals which were identified as euparin (**9**), mp 120 °C, identical with an authentic sample. Fractions 51 and 52, wt 2.2 g, exhibited two spots. These were separated by rechromatography into two apparently homogeneous fractions which polymerized on standing. Fractions 53–57, wt 5.8 g, also exhibited two spots and were combined. Rechromatography afforded 3.4 g of spicatin (**1a**), and 0.8 g of chapliatrin (**11**) as gums, ir, NMR, and TLC behavior identical with those of authentic samples. The later fractions were complex mixtures.

Extraction of *Liatris scabra*. Above-ground parts of *L. scabra* (Greene) K. Schum., wt 2.9 kg, collected by Dr. S. McDaniel on Oct 12, 1974, 1 mile northwest of Wahalak, Kemper County, Miss. (McDaniel no. 19406 on deposit in herbarium of Mississippi State University), was extracted with $CHCl_3$ in the usual manner. The crude gum, wt 15 g, was chromatographed over 600 g of silicic acid. Fractions 1–10 (benzene) eluted nothing. Fractions 11–18 (benzene–$CHCl_3$, 1:1) gave a complex mixture (TLC) whose components were not identified. Fractions 19–25 ($CHCl_3$) eluted 3.8 g of gummy material which exhibited one major spot on TLC. Further purification by TLC on silica gel ($PF_{254-355}$, solvent benzene–ethyl acetate, 1:1) gave a solid, wt 2.5 g, which was recrystallized from ethyl acetate and identified as eleganin (**10**) by melting point, mixture melting point, ir, and NMR spectrum. Fractions 26–35 ($CHCl_3$–MeOH) eluted nothing.

Extraction of *Liatris earlei*. Above-ground parts of *L. earlei* (Greene) K. Schum., wt 4.4 kg, collected by Mr. Robert Stewart on Oct 20, 1974, near Hobolochitto Creek 11 miles northwest of Polarville, Pearl River County, Miss. (Stewart no. 100 on deposit in herbarium of Mississippi State University), were extracted in the usual manner. The crude gum weighed only 7 g and exhibited several spots on TLC. Since different lactones from *Liatris* species frequently exhibit the same R_f, it was not possible to identify any lactone constituents in this way. Attempts to separate the components by preparative TLC using various solvent systems did not yield any homogeneous material.

Extraction of *Liatris pauciflora*. Above-ground parts of *L. pauciflora* Pursh, wt 5.9 kg, collected by Dr. R. K. Godfrey on Sept 8, 1972, 3 miles southeast of Orangedale along State Road 16, St. Johns County, Fla. (Godfrey no. 71997 on deposit in herbarium of Florida State University), was extracted with $CHCl_3$ in the usual fashion but gave a disappointingly low yield (8 g) of gum which contained a mixture of sesquiterpene lactones as revealed by TLC analysis. Column chromatography manner over silicic acid (Mallinckrodt 100 mesh) using benzene, benzene–$CHCl_3$, (3:1 and 1:1), $CHCl_3$, and $CHCl_3$–MeOH (2%) did not yield any homogeneous fractions.

Registry No.—**1a**, 53142-46-4; **3a**, 57576-26-8; **3b**, 58074-48-9; **4a**, 55306-05-3; **4b**, 55186-22-6; **4c**, 58074-49-0; **5**, 55051-66-6; **6**, 55051-67-7; **7**, 55051-68-8; **8a**, 55051-69-9; **8b**, 55051-70-2; **9**, 532-48-9; **10**, 57498-84-7; **11**, 58074-50-3.

References and Notes

(1) Part XI in a series "Constituents of *Liatris* Species". For part X, see W. Herz, I. Wahlberg, C. S. Stevens, and P. S. Kalyanaraman, *Phytochemistry*, **14**, 1803 (1975).

(2) This work was supported in part by Grant CA-13121 from the U.S. Public Health Service through the National Cancer Institute.

(3) W. Herz, J. Poplawski, and R. P. Sharma, *J. Org. Chem.*, **40**, 199 (1975). The tentative structures **1b** and **2b** suggested in this report were subsequently revised to **1a** and **2a** as the result of an x-ray analysis of spicatin hydrobromide (**3a**).[4]

(4) B. Karlsson, A.-M. Pilotti, A.-C. Wiehager, I. Wahlberg, and W. Herz, *Tetrahedron Lett.*, 2245 (1975). The preparation of **3a** is described in the Experimental Section.

(5) Assays in the KB (cytotoxicity) and PS (P-388 lymphocytic leukemia) systems were carried out under the auspices of Drug Research and Development, Chemotherapy, National Cancer Institute.

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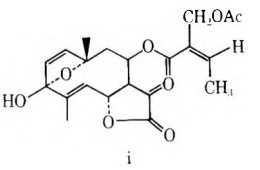
(7) An earlier study of *L. chapmanii* yielded the cytotoxic and antileukemic sesquiterpene lactone liatrin (i): S. M. Kupchan, V. H. Davis, T. Fujita,



i

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(9) It is not clear whether spicatin hydrochloride occurs naturally or is an artifact formed during the extraction process which employs refluxing chloroform. Other chlorine-containing guaianolides which have been isolated and could have arisen by similar opening of an epoxide ring are eupachlorin,[10] eupachlorin acetate,[10] eupachloroxin,[10] chlorohyssopifolin[11] (identical with centaurepensin),[12] and graminichlorin.[3]

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(14) In **4a**, **6**, or **8b**, the C-10 methyl resonance exhibits a chemical shift (1.73–1.75 ppm) characteristic of the *Z* rather than the *E* configuration if geraniol and nerol are taken as models.[15] This is clearly inappropriate; the downfield shift of ca. 0.1 ppm must be due to deshielding by the ester side chain on C-8 (compare **4a** with **8a**). Acetylation of the primary hydroxyl groups results in a small paramagnetic shift of the vinyl methyl signal (compare **4a** with **4b** and **8a** with **8b**), as might be expected for an *E* isomer. On the other hand, conversion to a trityl derivative produces a pronounced diamagnetic shift (compare **4a** with **4c**).

(15) See ref 16 of paper cited in ref 13.

(16) See ref 19 of paper cited in ref 13.

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Potential Antiandrogenic Antitumor Steroidal Lactones[1]

Gordon C. Wolf and Robert T. Blickenstaff*

Veterans Administration Hospital and Biochemistry Department, Indiana University School of Medicine, Indianapolis, Indiana 46202

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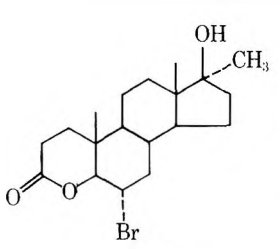
Steroids exhibiting antiandrogenic activity include 17α-hydroxyprogesterone caproate,[2] 17α-methyl-*B*-nortestosterone,[3] and cyproterone acetate.[4] These and most other antiandrogenic steroids suffer the disadvantage of also exhibiting varying degrees of progestational, estrogenic, and androgenic activity. An antiandrogenic steroid free of these undesirable activities is 6α-bromo-17β-hydroxy-17α-methyl-4-oxa-5α-androstan-3-one (**1**), having the special structural features of a 6α-bromine and a lactone ring.[5] Lactone rings, especially α-methylene lactone rings, are found in many naturally occurring antitumor compounds,[6] and in fact cytotoxic activity is reported for steroids having a lactone ring fused to the D ring, as in **2**.[7] Thus, the preparation of steroidal lactones takes on added significance in light of the numerous methods for converting γ-lactones into α-methylene-γ-lactones.[8-11]



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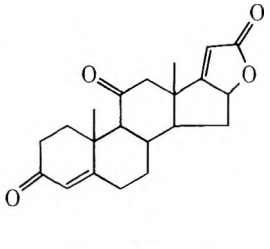
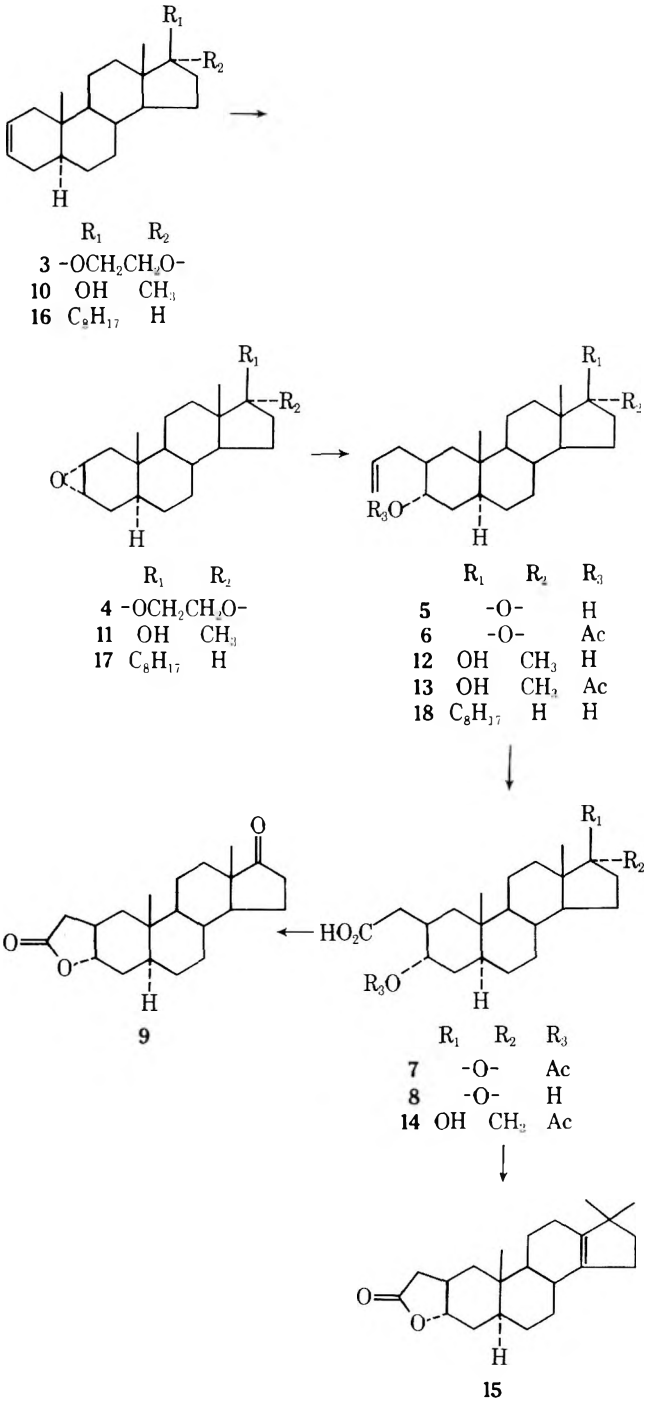


2

Lactones **9** and **15** were synthesized as outlined in Chart I. Thus, 2α,3-epoxy-5α-androstan-17-one ethylene ketal[12] (**4**) underwent normal ring opening[13] with allylmagnesium bromide to produce 2β-allyl-3α-hydroxy-5α-androstan-17-one (**5**) in 88% yield. Following the method of Huffman and Sobti,[14] oxidation of the acetate **6** with potassium permanganate, sodium periodate, and potassium carbonate in aqueous *tert*-butyl alcohol gave a 70% yield of 2-(3α-acetoxy-17-oxo-5α-androstan-2β-yl)acetic acid (**7**). Hydrolysis with potassium hydroxide in aqueous THF gave the hydroxy acid **8**, which was cyclized with perchloric acid in 78% yield to 2-(3α-hydroxy-17-oxo-5α-androstan-2β-yl)acetic acid lactone (**9**). The presence of the lactone ring is clearly shown by the 1780 cm^{-1} C=O band in the infrared spectrum.[15] The shape of the 3β-H (equatorial) resonance (3.85 ppm in **5**) suggests a narrow peak superimposed on a broad one,[16] and perhaps the presence of some 2β-H (axial), the result of C-2 attack by the allyl Grignard reagent, although all products (**5**, **7**, **8**, and **9**) gave single spots by TLC.

A similar sequence began with 17α-methyl-5α-androst-2-en-17β-ol (**10**), prepared by dehydrotosylation of 17α-methyl-5α-androstane-3β,17β-diol 3-tosylate in refluxing 2,6-lutidine (see Table I). *m*-Chloroperbenzoic acid produced the epoxide **11** in 76% yield. The Grignard reaction produced the 2β-allyl-3α-hydroxy derivative **12**; its acetate **13** was not purified but was used directly to prepare the acid **14**. Alkaline hydrolysis followed by acid-catalyzed ring closure gave 2-(3α-hydroxy-10,17,17-trimethyl-5α-gon-13-en-2β-yl)acetic acid lactone (**15**), a result of concomitant dehydration of the 17β-hydroxyl and rearrangement.[17] Either alternate structure, Δ^{16} unrearranged or Δ^{12} rearranged, would exhibit NMR resonance in the 6.1–5.5-ppm region, which **15** does not.

Chart I



Experimental Section[19]

2β-Allyl-3α-hydroxy-5α-androstan-17-one (5). Tosylation of isoandrosterone with tosyl chloride in pyridine gave a 90% yield of 3β-tosyloxy-5α-androstan-17-one, white crystals out of MeOH, mp 165–166 °C (lit.[12] 163–164 °C). Dehydrotosylation in refluxing lu-

Table I. Synthesis of a Steroidal Lactone

No.	Name	Yield, %	Mp, °C (solvent)	Ir, cm^{-1}	Anal., % Calcd	Anal., % Found
10	17α-Methyl-5α-androst-2-en-17β-ol[a]	67	154–155 (acetone)	3330 (OH), 1150, 935, 720, 660	C 83.27 H 11.18	83.24 11.22
11	2α,3-Epoxy-17α-methyl-5α-androstan-17β-ol[b]	76	206–208 (MeOH–H_2O)	3400 and 3330 (OH), 1155, 1076, 972, 936, 800	C 78.90 H 10.60	78.80 10.60
12	2β-Allyl-17α-methyl-5α-androstane-3α,17β-diol[c]	54	200–202 (acetone)	3390 (OH), 1632 (C=C), 1002 and 920 (–C=CH_2)	C 79.71 H 11.05	79.93 10.70
14	2-(3α-Acetoxy-17β-hydroxy-17α-methyl-5α-androstan-2β-yl)acetic acid	71	216–217 (benzene–hexane)	3425 (OH), 1738 (acetate C=O), 1698 (acid C=O), 1240 (acetate C=O)	C 70.90 H 9.42	71.08 9.51
15	2-(3α-Hydroxy-10,17,17-trimethyl-5α-gon-13-en-2β-yl)acetic acid lactone[d]	70	172–177 (dioxane–H_2O)	1795 (lactone C=O) 1210, 1199, 1139, 1059, 1000	C 80.44 H 9.82	80.31 10.01
18	2β-Allyl-5α-cholestan-3α-ol[e]	70	87–90 (amorphous, out of acetone)		C 84.04 H 12.28	84.43 12.23

[a] Prepared by dehydrotosylation of 17α-methyl-5α-androstane-3β,17β-diol 3-tosylate, mp 108–113 °c)lit.[20] 105–108 °C); compound **10** NMR δ 5.60 (s, 2 H, olefinic H at C-2 and C-3), 1.20 (s, 3 H, Me), 0.85 (s, 3 H, Me), 0.77 (s, 3 H, Me). [b] NMR δ 3.12 (m, 2 H, H's on C-2 and C-3), 1.18 (s, 3 H, Me), 0.82 (s, 3 H, Me), 0.77 (s, 3 H, Me). [c] NMR δ 6.1–5.4 (m, 1 H, βH of allyl group), 5.10 (broad s, 1 H, γ-H of allyl group), 4.88 (broad s, 1 H, γ-H of allyl group), 3.80 (broad s, 1 H, 3β-H), 1.17 (s, 3 H, Me), 0.82 (s, 6 H, Me's). [d] NMR δ 4.4–4.05 (m, 1 H, 3β-H), 0.95 (s, 6 H, Me's), 0.88 (s, 3 H, Me). [e] Prepared from 2α,3-epoxycholestane, mp 106–107 °C (lit.[21] 100–108 °C).

tidine for 2.5 h and recrystallization of the crude product from MeOH gave an 85% yield of 5α-androst-2-en-17-one, white plates, mp 108–109 °C (lit.[12] 104–111 °C). The latter was converted in 88% yield to the corresponding ethylene ketal **3**, white platelets: mp 117–118 °C (lit.[12] 112–113 °C); ir 3000 (olefinic CH), 1646 (C=C), 1300, 1165, 1110, 1052 cm^{-1}. Oxidation with *m*-chloroperbenzoic acid (85%) gave a 76% yield of 2α,3-epoxy-5α-androstan-17-one ethylene ketal (**4**), recrystallized from MeOH–H_2O: mp 152–156 °C (lit.[12] 151–152 °C); ir 1300, 1170, 1050, 1007, 948, 903, 800 cm^{-1}. Allylmagnesium bromide [prepared from 94 g (0.78 mol) of allyl bromide and 24.3 g (1 g-atom) of Mg] in 500 ml of Et_2O was added to a solution of 19.95 g (0.060 mol) of **4** in 400 ml of Et_2O. The mixture was refrigerated overnight, then excess reagent was destroyed with H_2O. The ethereal layer was washed and dried (Na_2SO_4); evaporation left an oil which was hydrolyzed in MeOH (500 ml) and H_2O (200 ml) containing 10 drops of concentrated HCl at reflux for 10 min. Cooling gave crude **5**, which was recrystallized in MeOH–H_2O to give an 88% yield of **5**: mp 142–147 °C; ir 3460 (OH), 3060 (olefinic CH), 1712 (C=O), 1632 (C=C), 1260, 1000, 896 cm^{-1}; NMR δ 6.0–5.5 (m, 1 H, β-H in allyl group), 5.08 (broad s, 1 H, γ-H in allyl group), 4.93 (broad s, 1 H, γ-H in allyl group), 3.85 (broad s, 1 H, 3β-H), 0.85 (s, 3 H, Me), 0.83 (s, 3 H, Me).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.82; H, 10.46.

2-(3α-Acetoxy-17-oxo-5α-androstan-2β-yl)acetic Acid (7). Acetylation of 4.627 g (0.014 mol) of **5** with acetic anhydride and pyridine at room temperature, followed by the usual work-up, gave **6**, an oil, which was oxidized without purification. A solution of 336 mg of $KMnO_4$, 29.96 g of $NaIO_4$, and 23.0 g of K_2CO_3 in 450 ml of H_2O was added to the oily **6** in 450 ml of *t*-BuOH, and the mixture was refrigerated overnight. Filtering, extraction with Et_2O, and acidification of the filtrate precipitated the crude product, which was recrystallized from benzene–petroleum ether to give 3.84 g (70%) of **7**, small needles: mp 263–264 °C; ir 1720 (acetate and ketone C=O), 1695 (acid C=O), 1240 (acetate C–O), 1200 cm^{-1}.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.89; H, 8.68.

2-(3α-Hydroxy-17-oxo-5α-androstan-2β-yl)acetic Acid (8). Hydrolysis of 3.84 g of **7** with KOH in aqueous THF at 45–50 °C for 24 h, acidification, extraction into $HCCl_3$, washing, and drying gave the crude product, which was recrystallized from benzene–hexane to give 2.23 g (65%) of **8**: mp 240–242 °C; ir 3460 and 3370 (OH), 1720 (ketone C=O), 1685 (acid C=O), 1250, 1020 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.29. Found: C, 72.51; H, 9.25.

2-(3α-Hydroxy-17-oxo-5α-androstan-2β-yl)acetic Acid Lactone (9). A solution of 1.74 g of **8** in 15 ml of THF and 75 ml of benzene containing 2 drops of $HClO_4$ was heated to reflux for 10 min, then concentrated to 25 ml volume, cooled, and diluted with 150 ml of hexane. Overnight refrigeration produced a crude product which was recrystallized in dioxane–H_2O to give 1.24 g (78%) of **9**: mp 172–173 °C; ir 1780 (lactone C=O), 1736 and 1720 (ketone C=O), 1208, 1141, 1094, 1022, 998 cm^{-1}; NMR δ 4.4–4.0 (m, 1 H, 3β-H), 0.91 (s, 3 H, 19-Me), 0.86 (s, 3 H, 18-Me).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.10; H, 9.24.

Registry No.—**3**, 14935-92-3; **4**, 10429-04-6; **5**, 57901-43-6; **7**, 57901-44-7; **8**, 57901-45-8; **9**, 57901-46-9; **10**, 3275-64-7; **11**, 968-54-7; **12**, 57901-47-0; **14**, 57901-48-1; **15**, 57901-49-2; **18**, 57901-50-5; isoandrosterone, 481-29-8; allyl bromide, 106-95-6; acetic anhydride, 108-24-7; 17α-methyl-5-α-androstane-3β,17β-diol, 1921-53-5; 2α-3-epoxycholestane, 1753-61-3.

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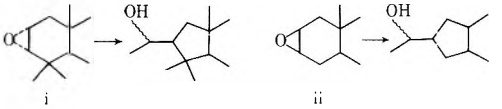

i ii

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Studies on the Terpenoids and Related Alicyclic Compounds. IV.[1] Dimerization of 14-Bromo-6-dehydroxysantoninic Acid

Koji Yamakawa* and Kiyoshi Nishitani

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

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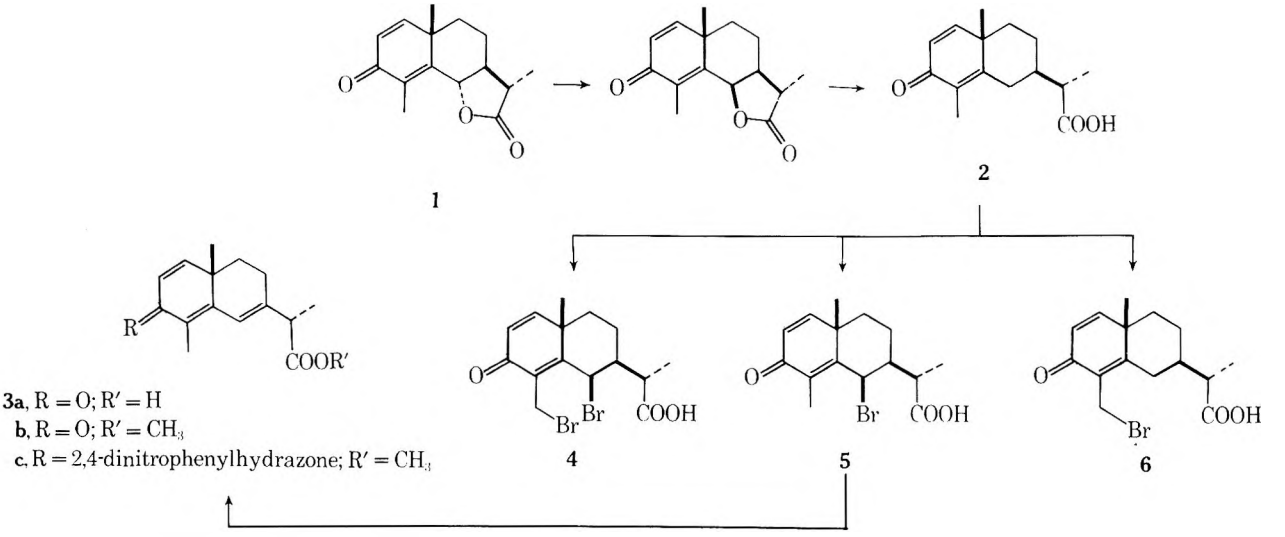
Previous studies in this laboratory have reported the transformation of α- and γ-tetrahydrosantonin into 5α- and 5β-2-oxosantanolide, respectively.[2] The original objective of the investigation outlined in this paper was the introduction of oxygenated functions at the C-8 position in the santan skeleton for the transformation of santan-6,12-olide into santan-8,12-olide.

For the above purpose, the preparation of trienonecarboxylic acid (3) from 6-dehydroxysantoninic acid (2) by bromination–dehydrobromination was investigated (Scheme I). This paper reports the formation of a novel 6-dehydroxysantonin dimer (7) during the course of this reaction.

Scheme I

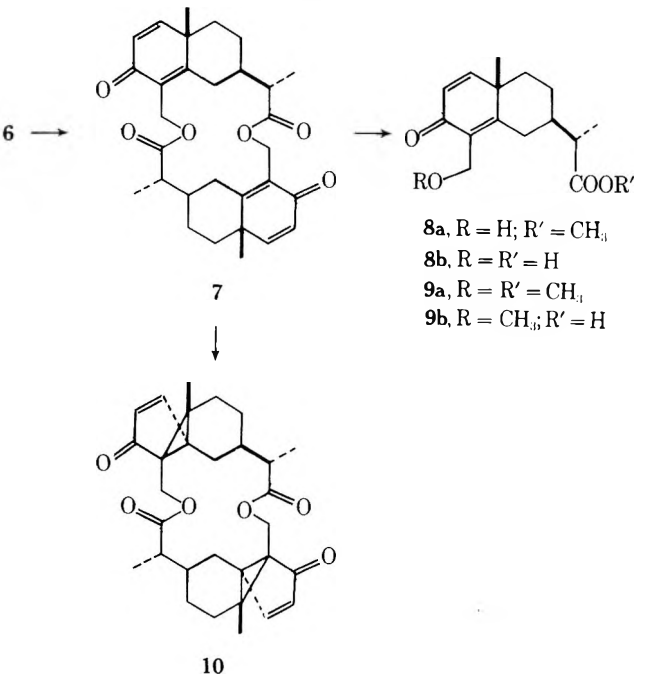


Miki[3] already reported that bromination of (±)-dienonecarboxylic acid (2) with *N*-bromosuccinimide in carbon tetrachloride gave a noncrystalline bromide, which was treated with 20% sodium carbonate in acetone and isolated without purification to give (±)-6-deoxysantoninic acid (3). Now, bromination of (−)-2, prepared from (−)-α-santonin (1),[4] was effected using *N*-bromosuccinimide in a carbon tetrachloride solution which was warmed at 40–45 °C until decoloration took place. After work-up, the residue was chromatographed on silica gel and purified by recrystallization. Fraction 1 gave a viscous oil, 6β,14-dibromide 4, whose structure was determined by ir, uv, and NMR data. The NMR spectrum of 4 showed absorption at δ 5.67 for the C-6 H and at δ 4.05 and 4.07 (AB-type doublets) for the C-14 methylene protons. Fraction 2 gave a crystalline product, mp 97–98 °C, whose structure was shown to be the 6β-bromide 5 by spectral data. The NMR spectrum of 5 indicated a peak at δ 5.61 (broad singlet, $W_{1/2}$ = 5 Hz) for the C-6 H. A viscous oily product, the 14-bromide 6, was isolated from fraction 3. Its structure was established by means of its mass spectrum, molecular ions $[M]^+$ 326 and 328, and ir and uv spectral data. The NMR spectrum of 6 showed signals at δ 4.22 and 4.48 (AB-type doublets) for the C-14 methylene protons.

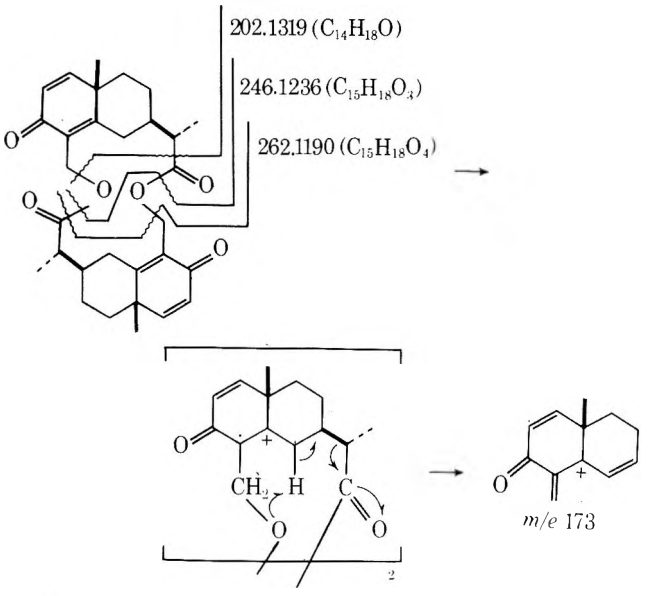
The 6β-bromide 5 was refluxed for 30 min with a 10% sodium carbonate in acetone solution. Work-up of the reaction mixture gave a pale-yellow, viscous oil, 3-oxo-1,4,6-trienic acid (3a), in 91% yield. The uv spectrum of 3a gave λ_{max} (EtOH) 232 and 316 nm (ϵ 12 860 and 12 830) characteristic of a triene chromophore.

The 14-bromide 6 was treated with 10% sodium carbonate in acetone solution as described above for the 6β-bromide 5. After work-up, the residue was recrystallized to give colorless needles, mp 310–312 °C. High-resolution mass spectral analysis of these crystals indicated an empirical formula of $C_{30}H_{36}O_6$, which suggested the structure to be the 6-dehydroxysantonin dimer (7) (Scheme II). The ir and uv spectrum of 7 revealed a cross dienone moiety, 1662, 1630, and 1610 cm^{-1} and λ_{max} (EtOH) 243 nm (ϵ 27 700). In the NMR spectrum of 7, C-10 and C-11 methyl protons appeared at δ 1.31 (singlet) and 1.18 (doublet), respectively, and AB-type doublet protons were indicated at δ 4.90 and 5.00 for the C-14 methylene group.

Scheme II



Scheme III. Mass Fragmentation Pattern for the 6-Dehydroxysantonin Dimer (7)



The mass fragmentation peaks of **7**, assigned by high-resolution measurement, also supported the dimeric structure **7**. The dimer **7** presumably undergoes fission of the bond connecting the two lactone centers to give the half-molecular ion of **7** at *m/e* 246 corresponding to $C_{15}H_{18}O_3$. Double elimination of the lactone of the dimer **7** occurs in a similar fashion as santonin shown by Budzikiewicz et al.[5] and illustrated in Scheme III. This gave the base peak of the spectrum at *m/e* 173 (*m/e* 246 − 73 ion). The dimer **7** also gave two ions at *m/e* 262 and 202 corresponding to $C_{15}H_{18}O_4$ and $C_{14}H_{18}O$, respectively. The ions at *m/e* 262 and 202 may be explained by cleavage of the C(12)–O and C(14)–O and C(11)–C(12) and C(14)–O bonds, respectively.

Hydrolysis of the dimer **7** with an alkaline methanolic solution gave a mixture of hydroxy keto acid **8b** and methoxy keto acid **9b**, which were converted to the corresponding hydroxy ester **8a** and the methoxy ester **9a**. The structures of **8a** and **9a** were confirmed by their NMR and mass spectra.

The photolysis of santonin under several conditions has been studied extensively by many workers.[6-12] Lumisantonin has been isolated as the initial photolytic rearrangement product of (−)-α-santonin. A solution of dimer **7** in dioxane was irradiated with a mercury lamp (300 nm) at room temperature. A lumisantonin type dimer (**10**) was isolated as colorless prisms, mp 310–312 °C. The structure of the lumisantonin type dimer **10** was confirmed by high-resolution mass spectroscopy for molecular ion $C_{30}H_{36}O_6$ (observed 492.2506) and half-molecular ion $C_{15}H_{18}O_3$ (observed 246.1227). The ir, uv, and NMR spectra of **10** showed λ_{max} (EtOH) 234 nm (ε 9200), ν_{CO} 1700 cm^{-1}, and C-1,1′ and C-2,2′ olefinic protons at δ 7.35 (d, *J* = 5) and 5.95 (d, *J* = 5 Hz), respectively, which also confirmed the presence of a lumisantonin type moiety.[8,13]

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. NMR spectra are for solution in $CDCl_3$ and they were measured with a JEOL JNM-4H-100 spectrometer at 100 MHz using Me_4Si as the internal standard. Ir spectra were measured with a Hitachi Perkin-Elmer Model 225 grating spectrophotometer. Uv spectra were measured for solution in ethanol with a Hitachi Model 323 spectrophotometer. Mass spectra were recorded on a Hitachi RMU-7M double-focusing mass spectrometer at 70 eV, by using direct insertion. High-resolution mass spectral data were determined with a Hitachi datalyzer 002 connected on line with the mass spectrometer. Specific rotations were measured for solution in chloroform with a Jasco DIP-SL digital polarimeter.

Gas–liquid phase chromatographic analyses were determined on a Shimadzu gas chromatograph, Model GC-3AF, equipped with a hydrogen flame detector, using a 1% SE-30 on Chromosorb W column. Wako silica gel C-200 (200 mesh) containing 2% fluorescence reagent 254 was used in column chromatography. Preparative thin layer chromatography was carried out using Merck silica gel HF_{254}.

6-Dehydroxysantoninic Acid (2). According to the procedure described by Piers et al.,[4] (−)-6-*epi*-α-santonin was reduced with zinc dust in methanol and glacial acetic acid. 6-Dehydroxysantoninic acid (**2**) obtained in 84% yield, had mp 101–102°; MS *m/e* (rel intensity) 248 $[M]^+$ (66), 230 $[M - H_2O]^+$ (37), 202 (22), 187 (25), 175 (100), 174 (80); $[\alpha]^{21}D$ −71° (*c* 0.6, $CHCl_3$); uv λ_{max} (EtOH) 241 nm (ε 9740); ir (KBr) ν 3200, 1740, 1660, and 1620 cm^{-1}; NMR δ 1.21 (s, 3, C-10 CH_3), 1.26 (d, *J* = 7 Hz, 3, C-11 CH_3), 1.88 (s, 3, C-4 CH_3), 6.27 (d, *J* = 10 Hz, 1, C-2 H), 6.74 (d, *J* = 10 Hz, 1, C-1 H).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.26; H, 8.11.

Bromination of the Keto Acid 2. A. To a solution of the keto acid **2** (800 mg, 3.2 mmol) in 120 ml of carbon tetrachloride was added *N*-bromosuccinimide (800 mg, 4.5 mmol). The reaction mixture was warmed to 40–45 °C under daylight for 6 h until decoloration took place. The reaction mixture was cooled and filtered. After the filtrate had been washed with water and dried, the solvent was removed under reduced pressure to give a pale-brown, viscous oil (1.14 g). The crude product was chromatographed on a silica gel column. Elution with *n*-hexane–ethyl acetate (5:1) gave three fractions. Fraction 1 gave 107 mg of a viscous oil, the 6β,14-dibromide **4**: MS *m/e* (rel intensity) 324, 322 $[M - (H_2 + HBr)]^+$ (17), 279, 277 $[M - (H_2 + HBr + COOH)]^+$ (13), 258 (35), 244 $[M - 2HBr]^+$ (100), 213 (39), 199 (95); $[\alpha]^{21}D$ −269° (*c* 0.8, $CHCl_3$); uv λ_{max} (EtOH) 255 nm (ε 10 810); ir ($CHCl_3$) ν 3500–2500 (broad), 1713, 1663, 1630, and 1610 cm^{-1}; NMR δ 1.34 (d, *J* , 7 Hz, 3, C-11 CH_3), 1.57 (s, 3, C-10 CH_3), 2.80 (m, 1, C-11 H), 4.05 (d, *J* = 10 Hz, 1, C-14 H_a), 4.70 (d, *J* = 10 Hz, 1, C-14 H_b), 5.67 ($W_{1/2}$ = 5 Hz, 1, C-6 H), 6.32 (d, *J* = 10 Hz, 1, C-2 H), 6.75 (d, *J* = 10 Hz, 1, C-1 H), 10.10 (1, COOH).

Fraction 2 gave 530 mg of a viscous oil which was a mixture of 6β,14-dibromide **4** and 6β-bromide **5** (5:4) as evidenced by NMR spectrometry.

Fraction 3 gave 160 mg of a viscous oil, the 14-bromide **6**: MS *m/e* (rel intensity) 328, 326 $[M]^+$ (3), 313, 311 (3), 282, 280 $[M - HCOOH]^+$ (2), 247 $[M - Br]^+$ (72), 246 $[M - HBr]^+$ (44), 201 $[M - (HBr + COOH)]^+$ (18), 174 (35), 173 (100); $[\alpha]^{21}D$ − 93° (*c* 0.7, $CHCl_3$); uv λ_{max} (EtOH) 241 nm (ε 10 000); ir ($CHCl_3$) ν 3500–2500 (broad), 1706, 1660, and 1625 cm^{-1}; NMR δ 1.24 (s, 3, C-10 CH_3), 1.28 (d, *J* = 6 Hz, 3, C-11 CH_3), 4.22 (d, *J* = 9 Hz, 1, C-14 H_a), 4.48 (d, *J* = 9 Hz, 1, C-14 H_b), 6.31 (d, *J* = 10 Hz, 1, C-2 H), 6.78 (d, *J* = 10 Hz, 1, C-1 H), 10.40 (1, COOH).

B. To a solution of the keto acid **2** (4.0 g, 16 mmol) in 400 ml of carbon tetrachloride was added 427 mg (2.4 mmol) of *N*-bromosuccinimide. The reaction mixture was warmed at 40–45 °C under daylight for 2 h. The reaction products (5.6 g) were separated in the same manner as described above. Fraction 1 gave 273 mg of the dibromide **4**.

Fraction 2 gave 1.73 g of 6β-bromide **5**, mp 91–93 °C. Recrystallization from *n*-hexane and ethyl acetate mixture gave colorless prisms: mp 97–98 °C; MS *m/e* (rel intensity) 326, 324 $[M - H_2]^+$ (1.7), 281, 279 $[M - COOH]^+$ (0.8), 246 $[M - HBr]^+$ (41), 244 (17), 201 $[M - (HBr + COOH)]^+$ (32), 174 (36), 173 (100); $[\alpha]^{21}D$ −194° (*c* 0.36, $CHCl_3$); uv λ_{max} (EtOH) 251 nm (ε 11 450); ir (KBr) ν 3400–3500 (broad), 1730, 1650, and 1618 cm^{-1}; NMR δ 1.35 (d, *J* = 7 Hz, 3, C-11 CH_3), 1.53 (s, 3, C-10 CH_3), 1.97 (s, 3, C-4 CH_3), 5.61 (broad s, $W_{1/2}$ = 5 Hz, 1, C-6 H) 6.26 and 6.70 (d, *J* = 10 Hz, 1 each, C-2 and C-1 H).

Anal. Calcd for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.85; Br, 24.42. Found: C, 54.64; H, 5.90; Br, 25.01.

Fraction 3 gave 1.52 g of a mixture of the 14-bromide **6** and the starting material **2** (1:1) as evidenced by NMR spectrometry.

Dehydrobromination of the 6β-Bromide 5. To a solution of the 6β-bromide **5** (600 mg) in 20 ml of acetone was added 8 ml of 10% sodium carbonate. The resulting solution was heated at the reflux temperature for 30 min. The reaction mixture was concentrated, treated with 10% sodium carbonate, and then extracted with ethyl acetate. The aqueous layer was acidified with hydrochloric acid and the mixture was extracted with ethyl acetate. After the extracts had been washed with water and dried, the ethyl

acetate was removed under reduced pressure, giving 410 mg (91%) of a pale-yellow, viscous oil, 3-oxo-1,4,6-trienic acid (**3a**). This crude trienoic acid (**3a**) was not purified further, but exhibited the following expected spectral properties: uv λ_{max} (EtOH) 232 nm (ϵ 12 860) and 316 (12 880); ir (film) ν 3500–2500 (broad), 1730, 1650, and 1600 cm^{-1}; NMR δ 1.16 (s, 3, C-10 CH_3), 1.41 (d, J = 7 Hz, 3, C-11 CH_3), 1.95 (s, 3, C-4 CH_3), 3.35 (q, J = 7 Hz, 1, C-11 H), 6.32 (d, J = 10 Hz, 1, C-2 H), 6.80 (d, J = 10 Hz, 1, C-1 H), 6.61 (broad s, 1, C-6 H), and 8.50 (1, COOH).

3a was esterified by treatment with excess etheral diazomethane. The crude product was purified by silica gel column chromatography, affording triene keto ester **3b** as a pale-yellow oil: bp 157–159 °C (7 mm); MS *m/e* (rel intensity) 260 $[M]^+$ (58), 245 $[M - CH_3]^+$ (28), 201 $[M - COOCH_3]^+$ (45), 185 (50), 173 (100); $[\alpha]^{21}D$ +273° (*c* 6.6, $CHCl_3$); uv λ_{max} (EtOH) 235 nm (ϵ 12 050), 310 (12 260); ir (film) ν 1735, 1655, 1615 cm^{-1}; NMR δ 1.16 (s, 3, C-10 CH_3), 1.38 (d, J = 7 Hz, 3, C-11 CH_3), 1.93 (s, 3, C-4 CH_3), 3.31 (q, J = 7 Hz, 1, C-11 H), 3.68 (s, 3, $COOCH_3$), 6.22 (d, J = 10 Hz, 1, C-2 H), 6.73 (d, J = 10 Hz, 1, C-1 H), 6.54 (broad s, $W_{1/2}$ = 4 Hz, 1, C-6 H).

The 2,4-dinitrophenylhydrazone of **3b** was obtained as deep-red plates (**3c**), mp 188–190 °C (from ethanol).

Anal. Calcd for $C_{22}H_{24}O_6N_4$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.76; H, 5.57; N, 12.77.

Treatment of 14-Bromide 6 with Sodium Carbonate. To a solution of 14-bromide **6** (400 mg) in acetone (20 ml) was added 10% sodium carbonate (8 ml). The solution was heated to reflux temperature for 1 h. The reaction mixture was concentrated and diluted with 10% sodium carbonate, and the extracted with ethyl acetate. The extracts were washed with water and dried. Evaporation of the solvent gave 60 mg (12%) of pale-yellow crystals. Recrystallization from ethanol or benzene gave colorless needles: mp 310–312 °C; mass spectrum $[M]^+$ 492.2506 (calcd for $C_{30}H_{36}O_6$, 492.2509), *m/e* (rel intensity) 492 $[M]^+$ (14), 477 $[M - CH_3]^+$ (95), 464 $[M - CO]^+$ (5), 262 (27), 246 $[M/2]^+$ (20), 202 (21), 173 (100); $[\alpha]^{21}D$ −214° (*c* 0.4, $CHCl_3$); uv λ_{max} (EtOH) 243 nm (ϵ 27 700); ir (KBr) ν 1725, 1662, 1630, 1610 cm^{-1}; NMR δ 1.18 (d, J = 7 Hz, 6, C-11,11′ CH_3), 1.31 (s, 6, C-10,10′ CH_3), 4.90 (d, J = 12 Hz, 2, C-14,14′ H_a), 5.00 (d, J = 12 Hz, 2, C-14,14′ H_b), 6.28 (d, J = 12 Hz, 2, C-2,2′ H), 6.78 (d, J = 10 Hz, 2, C-1,1′ H).

Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.14; H, 7.37. Found: C, 73.14; H, 7.50.

Hydrolysis of the Dimer 7. The dimer **7** (40 mg) was dissolved in a solution of potassium hydroxide (500 mg) in methanol (5 ml). The solution was stirred at room temperature for 5 h. The reaction mixture was acidified with hydrochloric acid and then extracted with ethyl acetate. The extracts were washed with water, saturated sodium bicarbonate, and water and dried. Evaporation of the solvent afforded 16 mg of pale-yellow oil. The oily product was a mixture of the hydroxy keto ester **8a** and the methoxy keto ester **9a**, which were identified by means of NMR spectroscopy.

The aqueous solution was acidified and extracted with ethyl acetate. The extracts were washed with water and dried and the solvent evaporated to give 28 mg of pale-yellow oil. The acidic oil, which was a mixture of hydroxycarboxylic acid **8b** and methoxycarboxylic acid **9b**, was not purified further but was treated with ethereal diazomethane. The products and proceeding neutral oil (16 mg) were combined. The viscous oil thus obtained was purified by preparative TLC (solvent hexane–acetone, 1:1).

Band 1 gave 17 mg of the methoxy keto ester **9a** as a pale-yellow oil: MS *m/e* (rel intensity) 292 $[M]^+$ (4), 277 $[M - CH_3]^+$ (31), 260 $[M - CH_3OH]^+$ (16), 201 $[M - (CH_3OH + COOCH_3)]^+$ (19), 173 (100); $[\alpha]^{21}D$ −78° (c 0.8, $CHCl_3$); uv λ_{max} (EtOH) 242 nm (ϵ 11 100); ir (film) ν 1735, 1660, 1630 cm^{-1}; NMR δ 1.20 (d, J = 7 Hz, 3, C-11 CH_3), 1.24 (s, 3, C-10 CH_3), 3.32 (s, 3, C-14 OCH_3), 3.70 (s, 3, $COOCH_3$), 4.25 (d, J = 10 Hz, 1, C-14 H_a), 4.29 (d, J = 10 Hz, 1, C-14 H_b), 6.25 (d, J = 10 Hz, 1, C-2 H), 6.72 (d, J = 10 Hz, 1, C-1 H).

Band 2 gave 15 mg of the hydroxy keto ester **8a** as a pale-yellow oil: MS *m/e* (rel intensity) 278 $[M]^+$ (2), 260 $[M - H_2O]^+$ (19), 201 $[M - (H_2O + COOCH_3)]^+$ (19), 173 (100); $[\alpha]^{21}D$ −52° (*c* 3.6, $CHCl_3$); uv λ_{max} (EtOH) 242 nm (ϵ 11 400); ir (film) ν 3440, 1730, 1660, 1625 cm^{-1}; NMR δ 1.21 (d, J = 7 Hz, 3, C-11 CH_3), 1.25 (s, 3, C-10 CH_3), 2.80 (1, OH), 3.70 (s, 3, $COOCH_3$), 4.46 (s, 2, C-14 CH_2), 6.25 (d, J = 10 Hz, 1, C-2 H), 6.80 (d, J = 10 Hz, 1, C-1 H).

Photolysis of the Dimer 7. A solution of 70 mg of **7** in 14 ml of dried dioxane was irradiated in a quartz probe at room temperature with a Rayonet preparative reactor RPR-208 (RUL-3000 Å). The solvent was removed in vacuo and the residue was subjected to preparative TLC (benzene–ethyl acetate, 1:1), which yielded 10 mg of colorless prisms, mp 261–262 °C (**10**). Recrystallization from ethanol gave colorless prisms: mp 263–265 °C, mass spectrum $[M]^+$ 492.2503 (calcd for $C_{30}H_{36}O_6$, 492.2509), *m/e* (rel intensity) 492 $[M]^+$ (1), 246 $[M/2]^+$ (20), 202 (12) 173 (81), 145 (70), 105 (55), 91 (100); uv λ_{max} (EtOH) 234 nm (ϵ 9200); ir (KBr) ν 1730, 1700 cm^{-1}; NMR δ 1.07 (s, 6, C-10,10′ CH_3), 1.08 (d, J = 7 Hz, 6, C-11,11′ CH_3), 4.10 (d, J = 12 Hz, 2, C-14,14′ H_a), 4.85 (d, J = 12 Hz, C-14,14′ H_b), 5.95 (d, J = 5 Hz, 2, C-2,2′ H), 7.35 (d, J = 5 Hz, 2, C-1,1′ H).

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Registry No.—**2**, 17974-84-4; **3a**, 57901-33-4; **3b**, 57901-34-5; **3c**, 57901-35-6; **4**, 57901-36-7; **5**, 57901-37-8; **6**, 57901-38-9; **7**, 57901-39-0; **8a**, 57901-40-3; **9a**, 57901-41-4; **10**, 57901-42-5; (−)-6-epi-α-santonin, 1618-78-6; *N*-bromosuccinimide, 128-08-5.

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Electrochemical Oxidation of Halomicin B to Rifamycin S

A. K. Ganguly,* P. Kabasakalian, S. Kalliney, O. Sarre, S. Szmulewicz, and A. Westcott

Chemical Research Department, Schering Corporation, Bloomfield, New Jersey 07003

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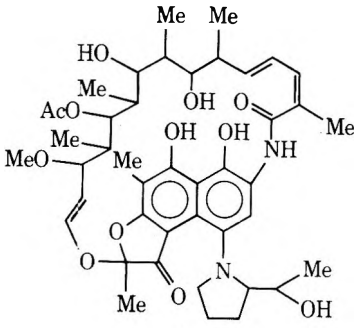
In an earlier communication[1] we have disclosed the structure of halomicin B (**1**). Elucidation of the structure of halomicin groups of antibiotics involves their conversion to a rifamycin S derivative and a substituted pyrrolidine base. Thus, the structural elucidation of halomicin B (**1**) involved its conversion into rifamycin S (**2**)[2] and a basic component (**3**).[1] In connection with the above-mentioned work, we have studied electrochemical oxidation of this group of antibiotics. It was conceived that halomicin B on electrochemical oxidation will lose two electrons easily and will be converted into a cationic species (**4**) which upon work-up will hydrolyze spontaneously into rifamycin S (**2**) and compound **3**. A similar cation (**4**) could also be produced from **1** in two steps: losing the first electron will yield a cation radical which could be trapped by a nucleophile (inter- or intramolecularly) into a radical followed by the loss of a second electron to the cation (**4**). The controlled potential[3] electrochemical oxidation of halomicin B was carried out in



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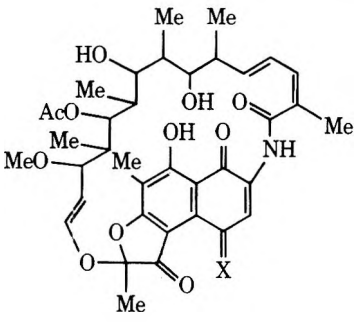
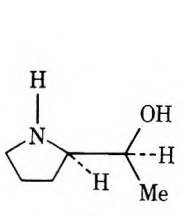


2, X = O
6, X = -OCH$_2$C(=O)—O—



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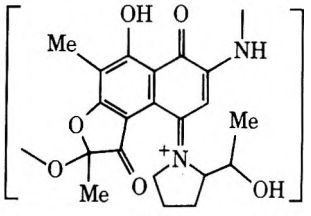

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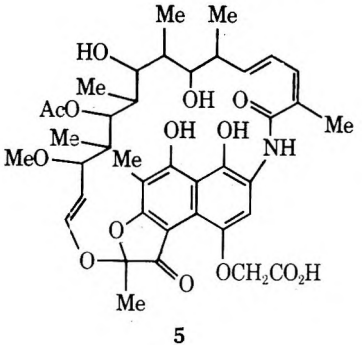
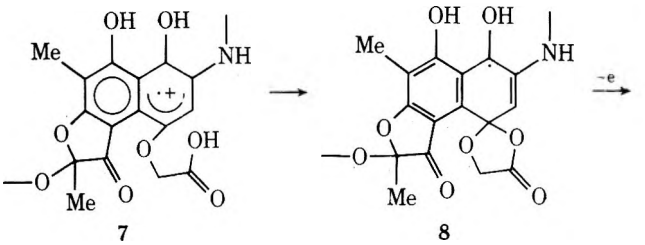


5

pH 4 buffer solution. The oxidation proceeds less efficiently at pH 6 and 7. After the oxidation was complete the reaction mixture was concentrated to a small volume. Extraction with chloroform followed by preparative TLC yielded pure rifamycin S (yield ~90%). The aqueous layer was basified and then extracted with ether to yield **3** (detected by TLC). Rifamycin B (**5**) on similar electrochemical oxidation was converted into rifamycin O (**6**) in a quantitative yield. This conversion could also proceed by the loss of two electrons directly or stepwise through the intermediacy of a radical cation (**7**) → radical (**8**) followed by its oxidation to the cation **9** which loses a proton to yield compound **6**.

During our work on the structural elucidation of halomicin B, we observed that preparative TLC (Analtech, silica gel GF) of rifamycin S (it is yellow in color as reported in the literature[2]) yielded a deep red colored crystalline compound which has been shown to have structure **10** and will be referred to in this communication as rifamycin S (red). Rifamycin S (red), $C_{37}H_{45}O_{12}N$: $[\theta]_{435}$ +25 000; λ_{max} 226



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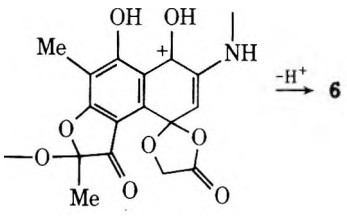

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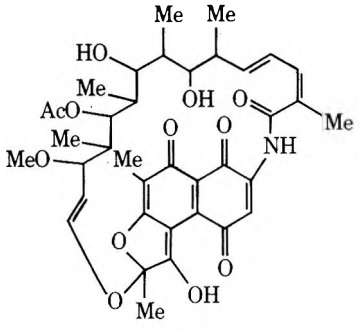

10

nm (ε 29 800), 265 (20 400), 312 (23 600), 532 nm (423); ν_{max} 3500, 3333, 1715, 1627, 1613 cm^{-1}. Rifamycin S (red) in THF solution when treated with a catalytic amount of acid was converted to rifamycin S (yellow). This interconversion suggested that the two compounds could be tautomeric. The NMR spectrum of rifamycin S (yellow) showed signals at δ 2.33 (aromatic methyl), H_3 at δ 7.8, and the hydrogen-bonded phenolic hydroxyl group at δ 12.5 whereas in rifamycin S (red) the aromatic methyl group appeared at δ 2.31 and H_3 at δ 7.64 and the signal at δ 12.5 was absent.[4] These results are consistent with the assigned structures **2** and **10** for rifamycin S yellow and red, respectively. Both these compounds have similar biological activities.

Experimental Section

Electrochemical Oxidation of Halomicin B (1) to Rifamycin S (2). A solution of halomicin B (100 mg) in a mixture of methanol and aqueous acetate buffer pH 4 (1:1 v/v) was deaerated for 1 h prior to oxidation using argon saturated with the above solvent mixture. The electrolysis was run at +0.3 V (vs. SCE) at 25 °C until there was no change in the integrated electrolysis current. The reaction mixture was concentrated to a small volume and then extracted with chloroform to yield rifamycin S (90 mg), shown to be identical with an authentic sample (mixture melting point, $[\alpha]_D$, uv, ir, NMR, and MS). The aqueous layer on basification and extraction with ether yielded **3** (detected by TLC and direct comparison with an authentic sample).

Electrochemical Oxidation of Rifamycin B (5) to Rifamycin O (6). It was carried out exactly as above and the yield of rifamycin O from rifamycin B was quantitative. The identity of rifamycin O was established by direct comparison with an authentic sample.

Registry No.—1, 54356-09-1; 2, 13553-79-2; 5, 13929-35-6; 6, 14487-05-9; 10, 57821-04-2.

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rent and a platinum working electrode cell [L. P. Rigdon and J. E. Harrar, *Anal. Chem.*, **46**, 696 (1974)] with aqueous pH 4 acetate buffer–methanol (1:1 v/v) in the salt bridge and the cathode compartment.

(4) NMR also shows the presence of exchangeable amide proton, thus ruling out other tautomeric structures.

Selective Reduction of the Amide Carbonyl Group in Dipeptides by Borane[1]

Roger W. Roeske,* Frederick L. Weitl, Kari U. Prasad, and Richard M. Thompson

Departments of Biochemistry and Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana 46202

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The facile reduction of amides by borane[2,3] led us to attempt the reduction of the peptide carbonyl group in *N*-alkoxycarbonyl dipeptide esters **1** in order to obtain the corresponding diamino esters **2**. The products, after hydrolysis of the ester and suitable protection of the newly generated amino group, can be regarded as derivatives of diamino acids **4** and could be incorporated into synthetic peptides. This would amount to selective replacement of a peptide bond by an aminoethylene unit (–CONH → –CH_2NH–) and would be useful in structure–activity studies in peptide hormones. The amino group also offers a point of attachment of a reactive group for affinity labeling of enzymes and receptors.

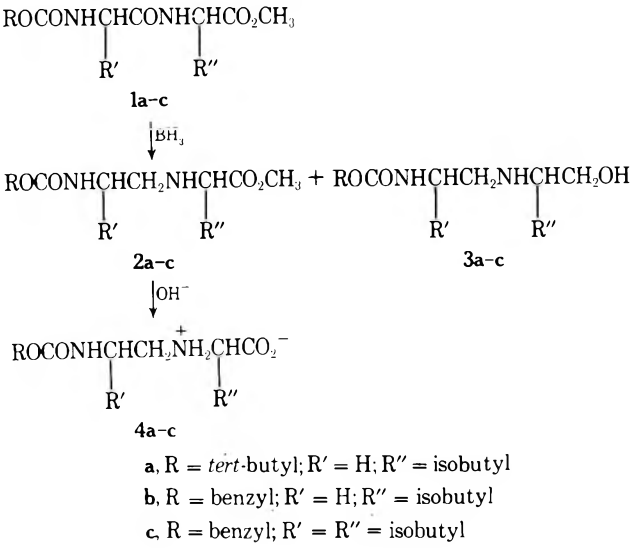
Since the relative ease of reduction of isolated carbonyl groups by BH_3 is $-CO_2H$ > $-CONR_2$ > CONHR > $-CONH_2$ > $-CO_2R$ > ROCONHR,[2-4] it was a priori possible to reduce selectively the amide bond in **1**. However, an ester group located α to an amide is more easily reduced to the corresponding alcohol than is an isolated ester. Thus when benzoyl glycine ethyl ester was treated with borane, the amino ester and amino alcohol were produced in yields of 11 and 85%, respectively.[3]

We have found that concurrent reduction of the ester in dipeptides is minimized by carrying out the reaction at −20 °C with 2 mol of BH_3 for 4–5 h. Under these conditions, a considerable amount of starting material remains unreacted, but it is easily separated from the basic products and does not diminish greatly the synthetic usefulness of the procedure. Thus, reduction of 3.0 g of Boc-Gly-Leu-OMe[5] under the above conditions gave 1.24 g of starting material and 0.64 g of pure **2a**, after separation from other products by chromatography on silica gel. Alkaline hydrolysis of **2a** gave the amino acid **4a** in 73% yield. In general, more vigorous reaction conditions led to more complex mixtures (TLC) from which only the amino alcohols **3** could be isolated.

We have found that the severe acid treatment used to hydrolyze the amine–borane complexes formed after reduction of simple amides[2] can be replaced by treatment with 0.5 N HCl in methanol at room temperature overnight, which is compatible with the benzyloxycarbonyl group. In fact, reductions of the acid-sensitive Boc dipeptide esters were quenched by treatment with aqueous methanol overnight.

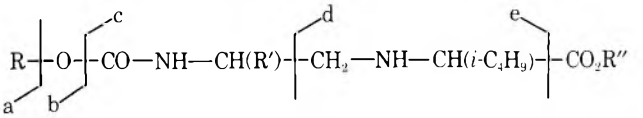
Although we expect the reduction to proceed with complete retention of asymmetry at the chiral centers, we have not proved this point. Perhaps the best evidence for retention is that the products from several reductions of the same material have the same optical rotations and have sharp melting points.

Scheme I



a, R = *tert*-butyl; R′ = H; R″ = isobutyl
b, R = benzyl; R′ = H; R″ = isobutyl
c, R = benzyl; R′ = R″ = isobutyl

The mass spectra of **2a–c** exhibit characteristic fragmentations which can be generalized as



Other ions may appear at M^+, M + 1, b + H, and e − (b + H), or may be due to losses of C_3H_6 (42 amu) or C_4H_8 (56 amu) via McLafferty rearrangements. The most interesting ion in these spectra is ion d. It was previously reported[6] that for polyamino alcohols formed by exhaustive reduction of peptides by $LiAlH_4$, the amine fragment formed by carbon–carbon cleavage was a significant ion in the mass spectra. However, in the present case the charge remains only on the carboxyl fragment.

Experimental Section

Melting points are uncorrected. TLC was carried out on silica gel plates (E. Merck) in BAW (*n*-BuOH–AcOH–H_2O, 4:1:1), TCW (tetrahydrofuran–cyclohexane–H_2O, 93:7:5), EAE (EtOAc–EtOH–AcOH, 9:1:1), and CMA ($CHCl_3$–MeOH–AcOH, 90:30:5); spots were located with ninhydrin and by chlorination followed by starch–iodide spray. Column chromatography was carried out on silica gel 60 (E. Merck) in a column 18 × 1 in. ^{1}H NMR spectra were taken in a Varian T-60 spectrometer. Mass spectra were determined on an LKB-9000-S at an ionization potential of 70 eV. Tetrahydrofuran was dried by distillation from CaH_2. Borane was obtained from the Aldrich Chemical Co. as a 1 M solution in THF containing 5 mol % $NaBH_4$ stabilizer. All evaporations were done at ≤40 °C. Microanalyses were by Midwest Microlabs, Indianapolis, Ind.

***N*-[2-[(*tert*-Butyloxycarbonyl)amino]ethyl]-L-leucine Methyl Ester Hydrochloride (2a).** A solution of 3.0 g (10 mmol) of Boc-Gly-Leu-OMe in 20 ml of THF was cooled to −20 °C in a flask flushed with N_2 and fitted with a rubber septum. A solution of 20 ml of 1 M BH_3 in THF (Aldrich Co.) was added with a syringe and the reaction was allowed to stir at −20 °C for 4 h under N_2. Residual BH_3 was quenched by cautious addition of 10 ml of MeOH at −20 °C (caution, H_2↑) and the mixture was stirred overnight at room temperature; the solution was evaporated under vacuum and treated with MeOH (3 × 50 ml) with evaporation to dryness after each addition, to remove boric acid as trimethyl borate. The residue was suspended in water, the pH was adjusted to 3.0 with HCl, and unreacted starting material (1.2 g) was removed by extraction with ether. The aqueous solution (mixture of **2a** and **3a**) was evaporated to dryness and chromatographed on a column of silica gel. **2a** was eluted with 5% MeOH in $CHCl_3$, followed closely by **3a**. Crystallization from MeOH–Et_2O gave 0.97 g of **2a**, mp 162–164 °C, in 30% yield (51% based on consumed **1a**): $[\alpha]^{25}$D +9.1° (c 1.0, MeOH); TLC (EAE) R_f 0.42; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.83 (s, 3 H, $COOCH_3$), 1.45 [s, 9 H, $-NHCOOC(CH_3)_3$],

0.95 [d, 6 H, $-CH_2CH(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 289 (M + 1, 0.7), 288 (M, 0.3), 229 (42) 215 (15), 173 (100), 158 (77), 155 (60), 113 (23), 102 (94), 99 (23), 73 (1.7), 57 (47). Anal. Calcd for $C_{14}H_{29}N_2O_4Cl$: N, 8.62. Found: N, 8.40.

***N*-[2-[(Benzyloxycarbonyl)amino]ethyl]-L-leucine Methyl Ester Hydrochloride (2b).** Z-Gly-Leu-OMe (10 mmol, 3.38 g) was treated with 20 ml of 1 M BH_3 in THF according to the procedure for **2a** except that the reaction was stopped after 5 h by the addition of 15 ml of 2 N HCl in MeOH. Work-up gave 1.4 g of starting material and 0.94 g of **2b** after recrystallization from MeOH–Et_2O: yield 26% (44% on basis of recovered **2a**); mp 160–162.5 °C; $[\alpha]^{25}D$ +15.9° (c 1, MeOH); TLC (EAE) R_f 0.46; ^1H NMR ($CDCl_3$, Me_4Si) δ 7.33 (5 H, C_6H_5), 5.13 (s, 2 H, $C_6H_5CH_2$), 3.77 (s, 3 H, $COOCH_3$), 0.95 [d, 6 H, $CH_2CH(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 323 (M + 1, 1.9), 322 (M, 1), 263 (100), 215 (1.2), 158 (76), 155 (88), 113 (52), 107 (28), 102 (77), 99 (47), 91 (80). Anal. Calcd for $C_{17}H_{27}N_2O_4Cl$: N, 7.83. Found: N, 7.71.

***N*-[L-2-[(Benzyloxycarbonyl)amino]-4-methylpentyl]-L-leucine Methyl Ester Hydrochloride (2c).** Z-Leu-Leu-OMe (10 mmol, 3.92 g) was treated with 20 mmol of BH_3 according to the procedure for **2b.** The ether extracts gave 3.1 g of starting material **1c.** Chromatography of the residue from the aqueous layer by the usual method gave **2c,** 0.30 g after recrystallization from MeOH–Et_2O: yield 7% (35% based on **1c** recovered); mp 162–164 °C; $[\alpha]^{25}D$ +2.0° (c 1, MeOH); TLC (EAE) R_f 0.74; ^1H NMR ($CDCl_3$, Me_4Si) δ 7.33 (5 H, C_6H_5), 5.10 (s, 2 H, $C_6H_5CH_2$), 3.75 (s, 3 H, $COOCH_3$), 0.93 [broad, 12 H, $CH_2CH(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 379 (M + 1, 0.6), 378 (M, 0.4), 319 (37), 271 (1.2), 211 (100), 169 (22), 158 (58), 155 (29), 107 (27), 102 (55), 91 (56). Anal. Calcd for $C_{21}H_{35}N_2O_4Cl$: N, 6.75. Found: N, 6.35.

***N*-[2-(*tert*-Butyloxycarbonyl)amino]ethyl]-L-leucine (4a).** A solution of 1.62 g of **3a** in 30 ml of MeOH and 11.0 ml of 1 N NaOH was allowed to stand at room temperature for 6 h, then concentrated under vacuum to a syrup, diluted with water, and adjusted to pH 6.5 with HCl. The precipitate was collected and washed with a little cold water, wt 1.00 g (73%). Anal. Calcd for $C_{13}H_{26}N_2O_4$: N, 10.21. Found: N, 9.97.

Registry No.—**1a,** 7535-69-5; **1b,** 17331-93-0; **1c,** 3504-37-8; **2a** HCl, 57901-23-2; **2b** HCl, 57901-24-3; **2c** HCl, 57901-25-4; **3a,** 57901-26-5; **4a,** 57901-27-6; BH_3, 13283-31-3.

References and Notes

(1) (a) Presented in part at the 65th Annual Meeting of the American Society of Biological Chemists, Minneapolis, Minn., June 1974. (b) We acknowledge support from the Grace M. Showalter Residuary Trust, the James Whitcomb Riley Memorial Association, and from Research Grant PHS RO1 ES 942-01.
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A Selective Phosphorylation by Means of Bis(*O*-thiocarbonyl) Disulfides and Triphenylphosphine

Hiroshi Takaku,* Machiko Yamana, and Yasuhiro Enoki

Laboratory of Organic Chemistry, Chiba Institute of Technology, Narashino-shi, Chiba-ken 275, Japan

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A number of phosphorylating systems have been devised with a view to preparing mixed diesters of phosphoric acid by intermolecular dehydration between monophosphates and alcohols. In order to bring the phosphate into reaction with an alcohol most systems employed initial activation of monophosphates by coupling reagents such as dicyclohexylcarbodiimide,[1] trichloroacetonitrile,[2] or 2,2′-dipyridyl disulfide and triphenylphosphine.[3] In these cases, mixed diesters of phosphoric acid, monophosphate, and pyrophosphate were formed so that the isolation of the expected mixed diesters of phosphoric acid became more difficult.

Recently, it has been demonstrated in this laboratory that phosphorylation of alcohols, phosphates, and nucleosides by the use of 8-quinolyl phosphates gave the corresponding mixed diesters of phosphoric acid, pyrophosphates, and nucleotides in good yields.[4]

The present paper describes a new method for the preparation of mixed diesters of phosphoric acid from monophosphate by the use of bis(*O*-thiocarbonyl) disulfides (**1**) and triphenylphosphine (**2**). The reaction seems to proceed through a phosphonium salt (**3**) which in turn reacts with monophosphate to form an intermediate (**4**), alcohol, and carbon disulfide. The intermediate (**4**) is further converted to phosphoryloxyphosphonium salt (**5**) by intramolecular oxidation–reduction reaction. The intermediate (**5**) reacts with alcohol to give mixed diester of phosphoric acid and triphenylphosphine oxide.

It is known that xanthic acid decomposes under acidic condition to give the corresponding alcohol and carbon disulfide.[5]

When *p*-nitrophenyl phosphate was treated with **1** and **2** at room temperature for 2 h, mixed diesters of phosphoric acid (**6**) were obtained in high yields without the formation of by-product such as symmetrical P^1,P^2-bis(*p*-nitrophenyl) pyrophosphate.

When *p*-nitrophenyl phosphate was treated with 5 equiv each of bis(*n*-butyl) dithiobis(thioformate) (**1c**) and **2** in dry tetrahydrofuran, *n*-butyl *p*-nitrophenyl phosphate (**6c**) was obtained in 85% yield.

Table I. Phosphorylation by Means of Bis(*O*-thiocarbonyl) Disulfides and Triphenylphosphine

Compd	Alkyl	Yield, %, of **6**	R_f value[a]
6a	Ethyl	84	0.82
6b	*n*-Propyl	82	0.84
6c	*n*-Butyl	85	0.86
6c	*n*-Butyl	83[b]	0.85
6c	*n*-Butyl	63[c]	0.86
6d	*n*-Pentyl	83	0.87
6e	Benzyl	76	0.86

[a] Paper chromatography was performed by the desending technique using Toyo Roshi No. 51 paper. Solvent system used was 2-propanol–concentrated ammonia–water, 7:1:2 (A). [b] Three equivalents each of reagents, bis(*n*-butyl) dithiobis(thioformate) and triphenylphosphine, were used. [c] One equivalent each of reagents, bis (*n*-butyl) dithioformate and triphenylphosphine.

Table II. Solvent Effects in Phosphorylation by Means of Bis(*n*-butyl)dithiobis(thioformate) and Triphenylphosphine

Solvent	Yield, %, of **6c**	Solvent	Yield, %, of **6c**
THF	85	Dioxane	76
Pyridine	85	CH_2Cl_2	80
DMF	67	$CHCl_3$	78
CH_3CN	70		

In a similar manner, various mixed diesters of phosphoric acid (6) were obtained in high yields (see Table I).

The effect of the solvent was examined in order to find a suitable condition for the preparation of **6c**. Of various solvents examined, it was found that the yield of **6c** decreased when dimethylformamide (DMF) is used as the solvent (see Table II).

In the above reactions, it was shown that the yields of **6** depend on the amount of **1** and **2**. As an example, when *p*-nitrophenyl phosphate was treated with 3 equiv each of **1c** and **2**, the result was almost the same as those obtained when 5 equiv each of **1c** and **2** were used. However, when 1 equiv each of **1c** and **2** were used, the yield of **6c** remarkably decreased (see Table I).

Finally, the synthesis of 3′-*O*-acetylthymidine 5′-ethyl phosphate was attempted. When 3′-O-acetylthymidine 5′-phosphate was treated with 3 equiv each of bis(ethyl) dithiobis(thioformate) (**1a**) and **2** in dry pyridine at room temperature for 8 h, the corresponding 3′-*O*-acetylthymidine 5′-ethyl phosphate was obtained in 98% yield.

In conclusion, it was noted that this type of phosphorylation was found to be effective for the preparation of pure mixed diesters of phosphoric acid in good yield under mild condition. Differing from the case of the phosphorylation with the use of dicyclohexylcarbodiimide, trichloroacetonitrile, or 2,2′-dipyridyl disulfide and triphenylphosphine, this reaction proceeds without the formation of by-product such as symmetrical pyrophosphate to afford the phosphorylated products in high yields.

Further studies on the synthesis of carboxylic esters are now in progress.

Experimental Section

Descending paper chromatography was performed on Toyo Roshi No. 51 or 51A paper using the solvent system 2-propanol–concentrated ammonia–water, 7:1:2 (solvent A), or 1-butanol–water–concentrated ammonia, 84:16:1 (solvent B). The R_f values of different compounds are given in Table I. Paper electrophoresis was performed in a high-voltage apparatus using Toyo Roshi No. 51A paper and 0.05 M phosphate buffer at pH 7 or 8. The phosphorus compounds were detected by means of a spray of Hanes–Isherwood reagent[6] on paper. Bis(ethyl) (**1a**), bis(*n*-propyl) (**1b**), bis(*n*-butyl) (**1c**), bis(*n*-pentyl) (**1d**), and bis(benzyl) dithiobis(thioformate) (**1e**) were prepared by the procedures in the literature.[7,8] *p*-Nitrophenyl phosphate was prepared by the method of Hata.[9] Triphenylphosphine was obtained from a commercial source and purified by recrystallization. 3′-O-Acetylthimidine 5′-phosphate was prepared by acetylation of thymidine 5′-phosphate with acetic anhydride in dry pyridine.

General Method. Reaction of *p*-Nitrophenyl Phosphate with Bis(*O*-thiocarbonyl) Disulfide and Triphenylphosphine. To a solution of *p*-nitrophenyl phosphate (21.9 mg, 0.1 mmol) and bis(*O*-thiocarbonyl) disulfide (1, 0.5 mmol) in dry tetrahydrofuran (1 ml), triphenylphosphine (**2**, 131 mg, 0.5 mmol) was added with vigorous stirring at room temperature for 2 h. To the reaction mixture, 1 ml of water was added and then the mixture was stirred at room temperature for several minutes. The mixture was then concentrated to dryness and the residue was dissolved in water (10 ml). Chromatography was performed on paper using solvent A and B for development. Yield of the compound **6** was determined spectrophotometrically using λ_{max} (H_2O) 291 nm (ϵ 10 000) (pH 7) for alkyl *p*-nitrophenyl phosphate (**6**). The results are summarized in Tables I and II.

3′-*O*-Acetylthymidine 5′-Ethyl Phosphate. To a solution of 3′-*O*-acetylthymidine 5′-phosphate (d-pTOAc, 0.5 mmol) and bis(ethyl) dithiobis(thioformate) (**1a**, 363 mg, 1.5 mmol) in dry pyridine (2.5 ml), triphenylphosphine (2, 393 mg, 1.5 mmol) was added and the mixture was kept standing at room temperature. After 8 h, water (5 ml) was added and then the solution was stirred at room temperature for several minutes. The mixture was then concentrated to dryness and the residue was dissolved in water (25 ml) and extracted with ether (three 20-ml portions). The aqueous layer was evaporated to dryness, and the residue was dissolved in water, converted into the sodium form, evaporated to dryness, and dissolved in dry methanol (10 ml). Addition of dry ether (200 ml) gave a precipitate which was collected and dried in vacuo to give 252 mg (98%) of 3′-*O*-acetylthymidine 5′-ethyl phosphate as a white solid: uv (pH 7) λ_{max} (H_2O) 268 nm (ϵ 9600). Paper chromatography (solvent A) R_f 0.72. Paper electrophoresis (0.05 M phosphate, pH 8) Rd-pT 0.54. Anal. Calcd for $C_{14}H_{20}PO_9N_2Na\cdot1.5H_2O$: C, 31.08; H, 4.29; N, 5.18. Found: C, 31.17; H, 4.35; N, 5.23.

Registry No.—**1a**, 502-55-6; **1b**, 3750-28-5; **1c**, 105-77-1; **1d**, 869-91-0; **1e**, 23363-97-5; **2**, 603-35-0; **6a**, 17659-67-5; **6b**, 18123-85-8; **6c**, 18123-87-0; **6d**, 29690-44-6; **6e**, 18123-91-6; d-pTOAc, 4304-30-7; *p*-nitrophenyl phosphate, 330-13-2; sodium 3′-*O*-acetylthymidine 5′-ethyl phosphate, 57821-08-6.

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Phosphorus Tribromide Promoted Allylic Rearrangement of a Tertiary Vinyl Carbinol. Stereochemistry of the Reaction Product and Application to the Synthesis of JH-25, a Potent Juvenile Hormone Mimic

James H. Babler

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

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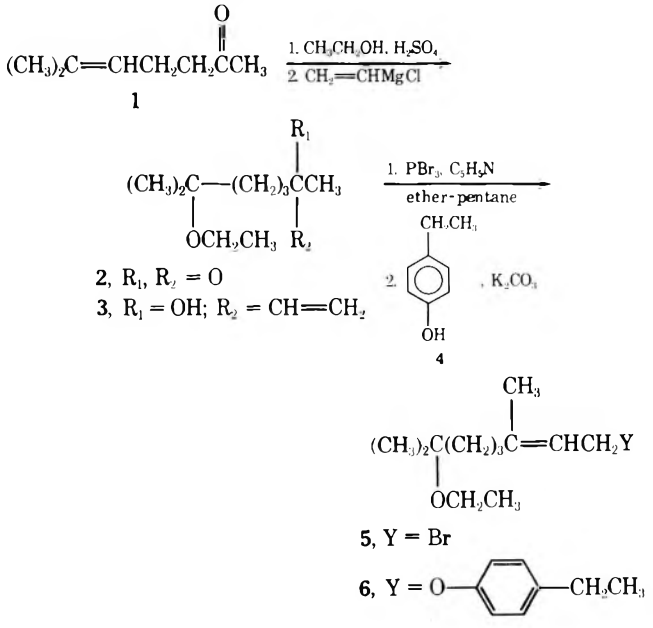
In recent years considerable attention[1] has been given to the possibility of controlling insect pests by interfering with the action of certain hormones that regulate normal

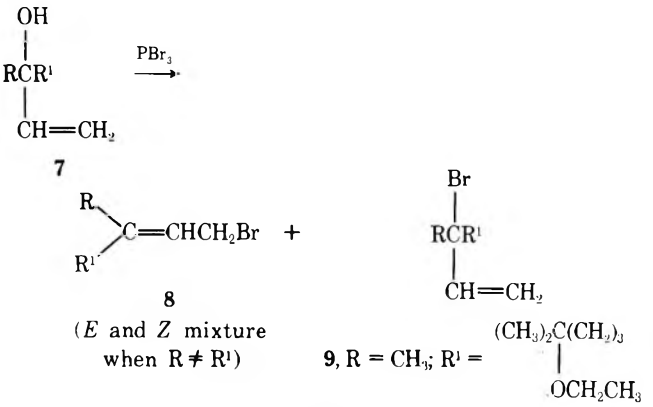
development. Interest in particular has been focused on methyl *trans,trans,cis*-10,11-epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate, which is one of two juvenile hormones occurring naturally in the silk moth *Hyalophora cecropia*.[2] In attempts to discover potentially more effective agents that possess activity similar to the latter chemical, a large number of organic compounds have been synthesized and evaluated as mimics of the natural product.[1] Among the more potent of the synthetic juvenile hormone mimics reported to date is 7-ethoxy-1-(*p*-ethylphenoxy)-3,7-dimethyl-2-octene (**6**) (called JH-25),[3] a facile synthesis of which is reported in this note.

In the previous synthesis[3] of JH-25 (**6**), the 7-ethoxy substituent was introduced in the last stage by a two-step process involving ethoxymercuration of 1-(*p*-ethylphenoxy)-3,7-dimethyl-2,6-octadiene, followed by demercuration using sodium borohydride. In order to expedite matters and avoid the problem of selective electrophilic addition to the latter diene, this same functionality was conveniently introduced at an early stage by acid-catalyzed addition of ethanol to the commercially available[4] 6-methyl-5-hepten-2-one (**1**). Although this reaction proceeded quite slowly in relationship to the corresponding methanolysis[5] of keto olefin **1**, 6-ethoxy-6-methyl-2-heptanone (**2**) could be obtained in approximately 60% yield after purification via fractional distillation. Subsequent addition of vinylmagnesium chloride to ketone **2**, followed by rearrangement of tertiary vinyl carbinol **3** using phosphorus tribromide, proceeded smoothly to afford the primary allylic halide **5**. The synthesis was completed by treatment of the latter (**5**) with *p*-ethylphenol (**4**) and potassium carbonate in acetone to yield, after purification by fractional distillation, JH-25 (**6**) in 54% overall yield from keto ether **2**. The NMR spectrum and physical properties of the final product were fully consistent with those previously reported[3] for this juvenile hormone mimic.

Scheme I



Since the *E* stereoisomer of JH-25 (**6**) is the one necessary for maximum biological activity, the stereochemistry of the final product was ascertained both by VPC and NMR analysis, and the *E*/*Z* ratio was found to be 75/25. Since the stereochemistry of the $\Delta^{2,3}$ double bond is determined during the allylic rearrangement of tertiary vinyl carbinol **3** to the primary allylic bromide **5**, these results indicate, not surprisingly, that such allylic transpositions



(i.e., **7** → **8**) do not necessarily proceed stereoselectively. Previous reports of this same type of rearrangement in the literature[6] fail to mention the stereochemistry of the rearranged double bond, although the implication is that it has the *E* (trans) configuration.

In an attempt to improve the yield and the stereoselectivity of the rearrangement step (**3** → **5**), the reaction was run at −70 °C and the results were compared with those obtained using a reaction temperature of −5 °C. The low-temperature reaction gave an increased material balance (92% vs. 79% when run at −5 °C), but the crude product contained approximately 30% of the unrearranged tertiary vinyl bromide **9**. Since the latter compound (**9**) affords a mixture of uncharacterized dienes in the next step of the synthesis, JH-25 (**6**) was produced in comparable yield in both cases. Furthermore, VPC and NMR[7] analysis indicated that the final product (**6**) was a 75:25 mixture of *E*:*Z* stereoisomers, irrespective of the temperature at which the rearrangement was effected.

Experimental Section[8]

6-Ethoxy-6-methyl-2-heptanone (2). Concentrated H_2SO_4 (7.0 ml) was added dropwise over a period of 10 min to an ice-cold solution of 16.94 g (134 mmol) of 6-methyl-5-hepten-2-one[4] in 51.5 ml (880 mmol) of absolute ethanol. After this mixture was stirred at room temperature for 70 h, it was poured into 400 ml of water and the product was isolated in the usual manner[8] by extraction with methylene chloride. Fractional distillation afforded 13.21 g (57%) of keto ether **2**: bp 51–55 °C (0.25 mm); 98% pure by VPC analysis,[9] oven temperature 133 °C, retention time 4.2 min; ν_{max} (film) 1715 (C=O), 1252, 1204, 1167, 1150, 1130, 1107, 1067, 945 cm^{-1}; δ_{Me_4Si} (CCl_4) 3.32 (quartet, J = 7 Hz, OCH_2CH_3), 2.06 (s, $O{=}CCH_3$), 1.11 (s, 6 H, geminal CH_3's), 1.09 ppm (t, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.71; H, 11.70. Found: C, 69.70; H, 11.70.

7-Ethoxy-3,7-dimethyl-1-octen-3-ol (3). A solution of 1.730 g (10.03 mmol) of ketone **2** in 6.0 ml of anhydrous ether was added dropwise over a period of 5 min to 6.0 ml of 2.2 M vinylmagnesium chloride–tetrahydrofuran solution, cooled to 0 °C in an ice water bath. After this mixture was stirred at 0 °C for 20 min, the reaction was quenched by dropwise addition of saturated aqueous NH_4Cl solution. Extraction[8] of the product with ether, followed by evaporative distillation, afforded 1.794 g (89%) of tertiary vinyl carbinol **3**: bp 60–73 °C (bath temperature, 0.08 mm); ν_{max} (film) 3460 (OH), 3115, 1635 (C=C), 1240, 1185, 1160, 1105, 1060, 985, 940, 905 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.87 ($CH{=}CH_2$, J_{AC} = 10, J_{BC} = 18 Hz), 5.29–4.85 ($CH{=}CH_2$, rest of ABC pattern[10]), 3.31 (quartet, J = 7 Hz, OCH_2CH_3), 1.22 (s, $HOCCH_3$), 1.10 (s, 6 H, geminal CH_3's), 1.10 ppm (t, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.76; H, 12.06.

1-Bromo-7-ethoxy-3,7-dimethyl-2-octene (5). A solution of 0.25 ml (2.63 mmol) of PBr_3 in 5.0 ml of anhydrous ether was added dropwise slowly over a period of 10 min to a solution of 560 mg (2.79 mmol) of tertiary vinyl carbinol **3** and 0.25 ml of dry pyridine in 15 ml of pentane and 10 ml of anhydrous ether, maintained at a temperature of −70 °C using a dry ice–isopropyl alcohol bath. After this mixture was stirred at −70 °C for 70 min, it was poured into 25 ml of ice water and the product was isolated[8] by extraction with pentane. To ensure removal of the pyridine, the extracts were washed twice with 5% (v/v) aqueous H_2SO_4. The yield[11] of color-

less oily bromide (**5** and **9**), too unstable to purify and therefore used directly in the next step, was 671 mg (92%): ν_{max} (film) 1655 (C=C), 1245, 1200, 1150, 1110, 1070, 950 cm^{-1}; δ_{Me_4Si} (CCl_4), 5.49 (t, J = 8.5 Hz, C=CH), 3.93 (d, J = 8.5 Hz, CH_2Br), 3.30 (quartet, J = 7 Hz, OCH_2CH_3), 1.78 ("Z" vinyl CH_3), 1.73 ("E" vinyl CH_3), 1.11 (s, 6 H, geminal CH_3's), 1.10 ppm (t, J = 7 Hz, OCH_2CH_3). NMR analysis indicated that approximately 30% of the bromide mixture consisted of tertiary vinyl bromide **9**, characterized by peaks at 6.33, 6.17, 6.05, and 5.88 ppm ($CH{=}CH_2$) as well as a singlet ($W_{1/2}$ = 1.4 Hz) at 1.83 ppm ($BrCCH_3$).

7-Ethoxy-1-(*p*-ethylphenoxy)-3,7-dimethyl-2-octene (6). A mixture of 666 mg (2.53 mmol) of crude bromide **5**, 3.5 ml of acetone, 350 mg (2.86 mmol) of 4-ethylphenol, and 1.36 g of anhydrous K_2CO_3 was stirred vigorously at room temperature for 15 h. Isolation of the product by extraction[8] with pentane, followed by fractional distillation, afforded 506 mg (66%) of JH-25 (**6**): bp 120–140 °C (bath temperature, 0.05 mm); >97% pure by VPC analysis,[9] oven temperature 225 °C, E/Z ratio 75/25, retention times 8.2 (Z), 9.4 min (E); ν_{max} (film) 1665 (C=C), 1610, 1578, 1505, 1240, 1225, 1167, 1105, 1065, 1000, 950, 817 cm^{-1}; δ_{Me_4Si} (CCl_4) 6.81 (AB quartet, 4 aryl H, peaks at 7.05, 6.91, 6.74, 6.59), 5.43 (t, J = 6 Hz, C=CH), 4.43 (doublet, J = 6 Hz, CH_2OAr), 3.27 (quartet, J = 7 Hz, OCH_2CH_3), 2.56 (quartet, J = 7 Hz, $ArCH_2CH_3$), 1.77 ("Z" vinyl CH_3), 1.71 (s, "E" vinyl CH_3), 1.09 (s, 6 H, geminal CH_3's), 1.08 ppm (t, J = 7 Hz, 2 CH_3).

Registry No.—**1**, 110-93-0; **2**, 51079-72-2; **3**, 57762-04-6; **4**, 123-07-9; **5**, 51079-70-0; (*E*)-**6**, 52730-76-4; (*Z*)-**6**, 57762-05-7; **9**, 57762-06-8; PBr, 7789-60-8.

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(7) The E/Z ratio was determined by integration of the signals for the vinyl methyl group. Chemical shift data for vinyl methyls in similar functionalized trisubstituted olefins have been previously reported. See R. B. Bates and D. M. Gale, *J. Am. Chem. Soc.*, **82**, 5749 (1960); K. Ogura, T. Nishino, T. Koyama, and S. Seto, *ibid.*, **92**, 6036 (1970).
(8) Reactions were carried out under a nitrogen atmosphere. Unless indicated otherwise, the isolation of reaction products was accomplished by pouring the mixture into water or saturated brine and extracting thoroughly with the specified solvent. The combined extracts were washed with 1 M aqueous NaOH and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed from the dried extracts by using a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The NMR spectra were recorded with a Varian A-60 NMR spectrometer and infrared spectra were obtained using a Beckman Acculab 1 spectrophotometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.
(9) A 6 ft × 0.125 in. SE-30 column was used for this analysis.
(10) Resolution of the signal peaks between δ 5.29 and 4.85 was not sufficient to allow a simple determination of J_{AB} and the chemical shifts for these two protons.
(11) When the reaction was run at −5 °C, the yield of crude bromide **5** was 79%, and none of the tertiary vinyl bromide **9** could be detected in the product.

Substitution at Phosphorus. The Unusual Effect of the Lithium Ion

W. S. Wadsworth, Jr.,* and R. L. Wilde

Department of Chemistry, South Dakota State University, Brookings, South Dakota 57006

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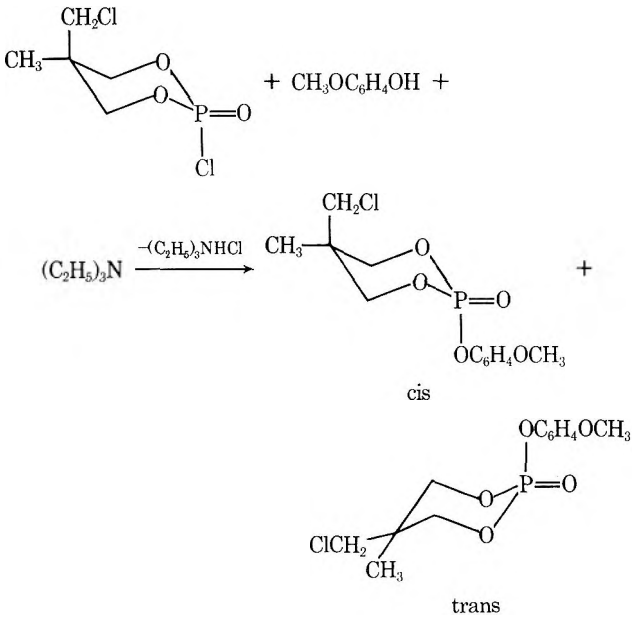
In previous papers we have shown that nucleophilic substitution at phosphorus in phosphates is strongly influenced by added cations.[1,2] We wish to report additional observations in this area and present a possible rationalization for them. As before, the conformationally immobile 2-substituted 5-chloromethyl-5-methyl-2-oxo- or 2-thio-1,3,2-dioxaphosphorinan systems were employed as substrates.[3] Inversion or retention at phosphorus upon substitution can conveniently be determined by NMR spectroscopy. Hydrogens on groups at the 5 position have different chemical shifts depending upon whether they are axial or equatorial.[4]

Table I

	Solvent	Added salt	Retention, %	Inversion, %
a	CH_3CN	0	8.8	91.2
b	CH_3CN	$LiClO_4$ (1 equiv)	96.1	3.9
c	CH_3CN	$Mg(ClO_4)_2$ (1 equiv)	0	100
d	CH_3CN	$KClO_4$ (1 equiv)	0	100
e	Benzene	0	40.8	59.2
f	CH_3CN	$LiClO_4$ (½ equiv)	88.3	11.7
g	Tetrahydrofuran	$LiClO_4$ (1 equiv)	78.6	21.4
h	CH_3CN	$(C_2H_5)_3N^+CH_2C_6H_5Cl^-$ (1 equiv)	38.4	61.6
i	CH_3CN	$(C_2H_5)_3N^+CH_2C_6H_5Cl^-$ (1 equiv) + $LiClO_4$ (1 equiv)	94.5	5.5
j	CH_3CN	LiCl (1 equiv)	87.5	12.5

We have found that we can control the stereochemical pathway in at least one system (Scheme I) by the judicious selection of the cation, Table I.

Scheme I



The combined product yields are greater than 90% with the product ratio unaffected by work-up procedures. The small yield of minor isomer in those cases where it is obtained may be due to prior isomerization of starting material by chloride ion formed as by-product. Thus, under identical reaction conditions the phosphorochloridate is slowly isomerized by slightly soluble triethylammonium chloride with 3 days required to establish equilibrium. In contrast substitutions are over in a matter of minutes. Prior isomerization would be expected in h where a soluble quaternary chloride is employed.

Strangely, the starting phosphorochloridate does not isomerize when triethylamine is added to acetonitrile or chloroform solutions. This behavior contrasts with the ac-

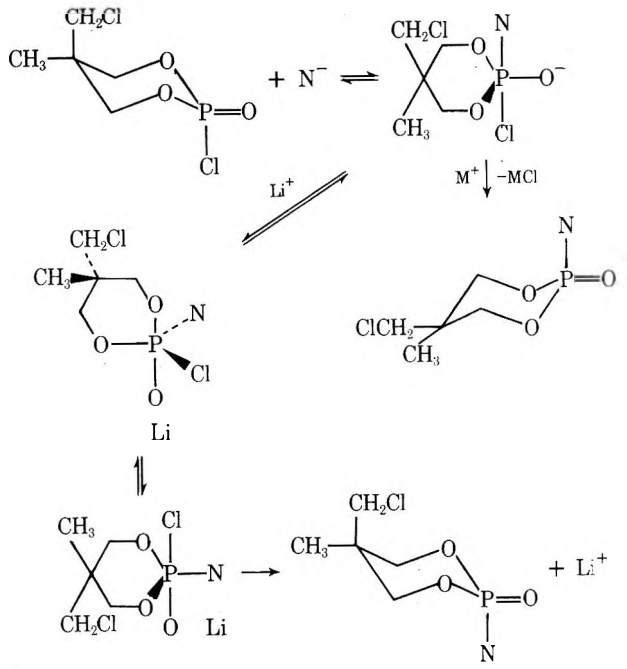
tion of pyridine, which promotes almost istantaneous isomerization and heat evolution. The products are stable under reaction conditions. The ratios are unaffected upon addition of product to acetonitrile–triethylamine–salt mixtures, evidence that product formation is kinetically controlled.

Without added salt, inversion predominates and is apparently aided by the ammonium salt formed as a by-product. Indeed, in the case of a less polar solvent, benzene, in which the by-product is less soluble and effective than in acetonitrile, retention competes. The ability of cations, other than lithium ion, to promote the inversion route is apparent from c and d. As pointed out in a previous publication,[1] tetramethylammonium and sodium salts have an effect on the mode of substitution which is similar to that of the soluble potassium and magnesium salts included in Table I.

Surprisingly, added lithium ion in the form of its soluble salts effects substitution in a manner directly opposite to that of other cations tested; retention is nearly 100%, b. The unusual effect of the lithium ion is further demonstrated by its ability to overcome any possible effect exerted by an added soluble salt, i. It is effective in less than equivalent concentrations, f, and although diminished, its ability to divert the reaction to retention prevails in a solvent in which it would be expected to be at least partially solvated, g, or sparingly soluble, j. From spectral data, ir and NMR, we can find no evidence of bonding between substrate and cation. Spectra taken in acetonitrile are essentially identical irrespective of the salt added. Thus added cations listed in Table I most likely exert their influence during the course of the substitution and do not alter the structure of the reactant.

To explain our observations we propose a scheme which is a modification of our original and similar to that recently put forth by others (Scheme II).[5] We assume two competing pathways. Cations, other than lithium, act as electrophiles toward the chloride ion aiding its departure and inversion. It is not unlikely that the catalyzed inversion process entails partial bond breakage prior to complete bond formation and that a formal trigonal bipyramid intermediate may not form.

Scheme II[a]



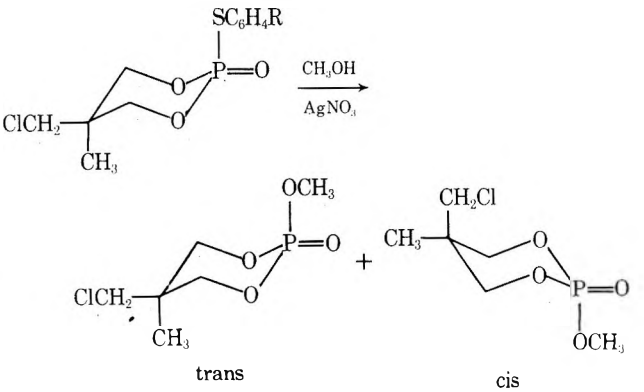
[a] Ring conformation has been neglected.

In the absence of cation effects, the retention pathway via pseudorotational permutations of the initially formed intermediate is of lower energy. Singly bonded oxygen has a preference for an equatorial position, a condition met for all three alkoxy groups by the retention pathway.[6] Lithium ion, with its affinity toward oxygen and small ionic radius, may bond with negatively charged oxygen thereby enhancing the preference for an axial position by the original phosphoryl oxygen. Further, as a consequence of bonding with lithium, the P–O bond may be lengthened and P–Cl bond strengthened[7] thereby reducing the effectiveness of extraneous cations and rendering the inversion pathway less favorable.

We have observed that the influence of lithium ion is independent of the leaving group. Either pure cis or trans 2-*p*-nitrophenyl esters in the presence of lithium ion undergo substitution predominantly by retention whereas in the presence of other salts, both geometric isomers of the product are produced with that from inversion in excess. In those cases where inversion is the only pathway, i.e., methanolysis of the starting phosphorochloridate, the lithium ion is unique in its ability to effect a sharp decrease in the substitution rate.[8] The fact that inversion is the only pathway for solvolysis may reflect the ability of a protic solvent to aid in the removal, by means of hydrogen bonding, of the chloride ion.

Of further possible bearing is our observation that *trans*-2-thiophenyl-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan undergoes substitution completely via retention, a situation which prevails in the absence of salts or in the presence of those cations which are not expected to coordinate strongly to sulfur.[9] Only the trans methyl ester[10] is produced (Scheme III) with its rate of formation dependent upon the substituent, R, in a predictable manner. In the presence of silver or mercury salts, however, where coordination between cation and leaving group is a possibility, the cis methyl ester, produced via inversion, predominates.[8] Thus, as we propose, there is a distinct possibility that coordination of cations with leaving groups promotes inversion whereas in the absence of such effects, retention is favored.

Scheme III



trans cis

Experimental Section

General. NMR spectra were recorded on a Varian A-60A spectrometer with deuteriochloroform as solvent and tetramethylsilane as an external standard. Isomer ratios were obtained by interpretation of peaks due to hydrogens on either axial or equatorial 5-methyl groups; axial CH_3 1.29 ppm, equatorial CH_3 0.97 ppm.

Starting Materials. The phosphorochloridate was prepared as previously described[4] and recrystallized (CCl_4) just prior to use. Before their employment, salts were thoroughly dried and stored under anhydrous conditions. *p*-Methoxyphenol was the reactant of choice owing to the ease of product work-up. Other nucleophiles including phenol gave similar results under the various conditions.

2-*p*-Methoxyphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan. A solution of phosphorochloridate (2.18 g, 0.01 mol) and lithium perchlorate (1.06 g, 0.01 mol) in 10 ml of dried, freshly distilled acetonitrile was added to a solution of *p*-methoxyphenol (1.24 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in 10 ml of the same solvent. The solution was stirred at room temperature for 2 h and added to 200 ml of H_2O. The crystalline solid was removed by suction filtration, washed well with water, and dried. The product was recrystallized from carbon tetrachloride without undergoing a change in isomers ratio, 2.65 g (92.7%), 96.1% cis, 3.9% trans.

Anal. Calcd for $C_{12}H_{16}ClO_5P$:[11] C, 50.35; H, 5.59; Cl, 12.24. Found: C, 50.46; H, 5.52; Cl, 12.38.

This procedure is typical of those used to obtain the ratios of Table I.

Registry No.—*cis*-2-*p*-Methoxyphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-31-9; *trans*-2-*p*-methoxyphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan 36912-32-0; *trans*-2-chloro-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 28097-07-6; *p*-methoxyphenol, 150-76-5; $LiClO_4$, 7791-03-9; $Mg(ClO_4)_2$, 13770-16-6; $KClO_4$, 7778-74-7; $(C_2H_5)_3N^+CH_2C_6H_5Cl^-$, 56-37-1; *trans*-2-thiophenyl-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-44-4; *trans*-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-27-3; *cis*-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 28097-12-3.

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(7) The fact that Mg^{2+} does not parallel the lithium ion in its effect may be due to its higher coordination number. No attempt was made to remove waters of coordination from the salt.
(8) Unpublished results.
(9) Our original observation, ref 4, of substitution with 100% retention in the case of *S*-phenyl phosphorothioates has recently been extended to a similar *S*-alkyl system: T. D. Inch, G. J. Lewis, R. G. Wilkenson, and P. Watts, *J. Chem. Soc., Chem. Commun.*, 500 (1975).
(10) The NMR spectra of the methyl esters and their preparation by another route has been reported, ref 4.
(11) Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

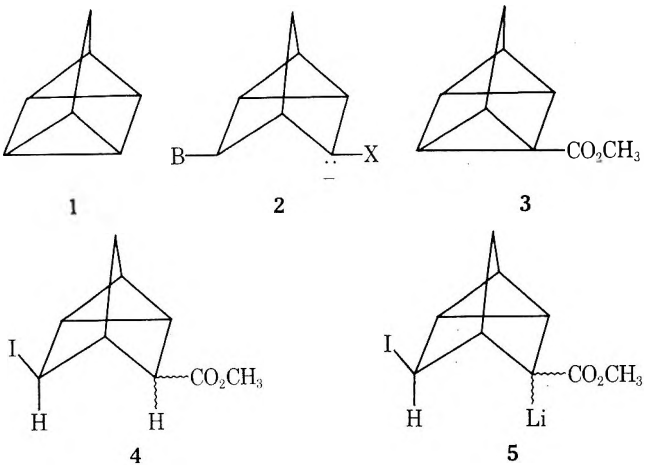
Addition of Lithium Iodide to a Strained Carbon–Carbon σ Bond. In Situ Protonation, Methylation, and Benzylation of the Adduct

Gerald F. Koser* and Attila G. Relenyi

Department of Chemistry, The University of Akron, Akron, Ohio 44325

Received September 22, 1975

Tetracyclo[3.2.0.$0^{2,7}$.$0^{4,6}$]heptane (**1**) has emerged as a useful substrate for the study of nucleophilic additions to strained carbon–carbon σ bonds. When electrophilic substituents are attached at C-1, the 1–7 bond becomes vulnerable to nucleophilic cleavage, under mild reaction conditions.[1a,b,2,3] It seems likely that such reactions proceed through nortricyclyl anions of general structure **2**, their

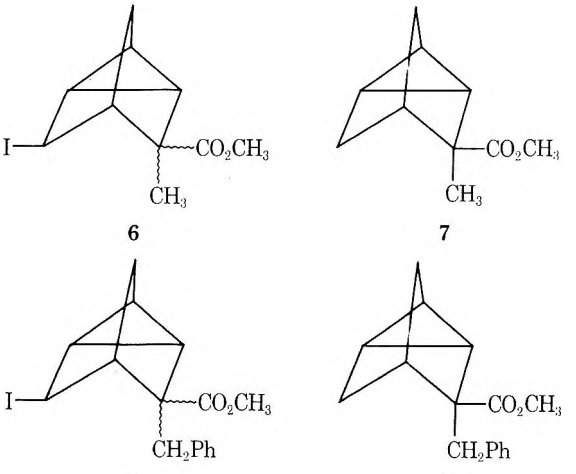


1 2 3 4 5

ease of formation being determined by the ability of the attached group X to stabilize adjacent negative charge.[2] However, until now those anions have been intercepted only by protonation, even when acetonitrile was the sole proton source.[3] This research was initiated with the objective of trapping **2** with alkylating agents, and, to that end, the iodide opening of 1-carbomethoxyquadricyclene (**3**) was chosen as a model reaction.

Our first task, then, was to demonstrate the feasibility of 1–7 bond cleavage in **3** by iodide ion, and, accordingly, **3** was allowed to react with lithium iodide in acetonitrile. Following work-up, a 43% yield of crude 3-carbomethoxy-5-iodonortricyclene (**4**), epimeric at C-3, was obtained.[4] The structure of **4** was inferred from its elemental composition and spectra (ir, near ir, NMR). Specifically, the 60-MHz ^1H NMR spectrum of **4** displays a complex 7 H multiplet at high field, a carbomethoxy singlet at δ 3.67, and a pair of broad singlets at δ 3.92 and 4.10 which we assign to H-5 of the individual epimers.

It seems likely that 3-lithio-3-carbomethoxy-5-iodonortricyclene (**5**) is an *intermediate* in the above reaction. Indeed, a successful in situ methylation of **5** has been achieved. When a solution of **3** in THF was added dropwise to a solution of lithium iodide in iodomethane–THF, a mild, exothermic reaction ensued. Following work-up, a 74% yield of *crude* 3-methyl-3-carbomethoxy-5-iodonortricyclene (**6**) was obtained as a yellow oil. Unfortunately, while **4** is stable in air, **6** rapidly turns green, and the precipitation of a black, amorphous solid follows. The 60-MHz ^1H NMR spectrum of **6** is similar to that of **4** except that it exhibits a carbon-bound methyl singlet at δ 1.23. However, we have been unable to obtain a *completely* satisfactory ^1H NMR spectrum of **6**. The carbomethoxy singlet invariably



6 7 8 9

appears to be 20–30% more intense than the methyl singlet. We think that this is due to the presence of an impurity (possibly **4**) with a carbomethoxy group but not a carbon-bound methyl group which is not eliminated by our isolation techniques. In any event, we sought to substantiate our NMR assignments and subjected **6** to reductive deiodination with zinc in methanol. The reaction was not clean but 3-methyl-3-carbomethyoxynortricyclene (**7**) was a major product and was isolated in small quantity from an Apiezon L column. In the 60-MHz ^1H NMR spectrum of **7**, the carbomethoxy singlet appears to be a little more intense than the methyl singlet, but in the 300-MHz spectrum, they are clearly of equal intensity.

The lithium iodide adduct of **3** can also be benzylated. When a solution of **3** in THF was added to a solution of lithium iodide and benzyl iodide in THF, *crude* 3-carbomethoxy-3-benzyl-5-iodonortricyclene (**8**) was isolated in ~80% yield. When **8** was subjected to the action of zinc in methanol, reductive deiodination occurred, but the product mixture was extremely complex. Even so, the major product (~30–40%), 3-carbomethoxy-3-benzylnortricyclene (**9**), was purified by distillation and characterized by elemental, ir, and NMR analysis.

Finally, in control studies, it was shown that **3** does not react with either iodomethane or benzyl iodide in the absence of lithium iodide.

Experimental Section

General. ^1H NMR spectra (60 MHz) were recorded on a Varian Model A-60 NMR spectrometer (relative to internal Me_4Si), infrared spectra on a Perkin-Elmer Model 337 spectrophotometer, and near infrared spectra on a Cary 17 uv–visible–ir spectrophotometer. NMR spectra (300 MHz) were recorded on a Varian Model HR-300 NMR spectrometer at The University of Akron's NMR Center. GLC analyses and collections were conducted on a Hewlett-Packard F and M Model 700 Scientific gas chromatograph, a 6 ft × 0.25 in. column of Apiezon L being utilized. Elemental compositions were determined by Galbraith Laboratories, Inc., Knoxville, Tenn. The lithium iodide (99+% pure, anhydrous reagent) employed in these studies was purchased from Ventron and was pumped under vacuum just prior to use, a procedure which caused the salt to change in color from tan to off-white. Benzyl iodide was prepared by the action of sodium iodide in acetone on benzyl chloride and was distilled. Some of it was a gift from Mr. Gary Linden of this department. THF was distilled either from lithium aluminum hydride or lithium triphenylmethide just prior to use. Iodomethane was distilled from anhydrous magnesium sulfate and used directly.

Reaction of 3 with Lithium Iodide in Acetonitrile. A solution of **3** (1.50 g, 9.98 mmol) in CH_3CN (5 ml) was added dropwise to a solution of lithium iodide (2.0 g, 14.9 mmol) in CH_3CN (20 ml). The reaction mixture was allowed to stir for 2 h under nitrogen at room temperature and was then concentrated in vacuo to a dry white solid. The solid was treated with water (50 ml) and extracted with three 25-ml portions of CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo and yielded 1.2 g (43%) of crude 3-carbomethoxy-5-iodonortricyclene (**4**) as a yellow oil. The crude oil was subjected to column chromatography (silica gel, CH_2Cl_2) followed by preparative TLC (silica gel, CH_2Cl_2) and reisolated as a clear, colorless oil.

Anal. Calcd for $C_9H_{11}IO_2$: C, 38.87; H, 3.99. Found: C, 39.00; H, 4.02.

Spectroscopic Data for 4. Ir (neat) 3.38 (CH), 3.26 (sh, cyclopropyl CH), 5.74 (C=O), 12.15 μ (nortricyclene skeleton);[5a-c] near ir (CH_2Cl_2) λ_{max} 1.653 μ (ϵ 1.143) (first C–H stretching vibration overtone characterisitic of nortricyclenes);[6] NMR ($CDCl_3$) δ 4.10 and 3.92 (broad singlets, H-5), 3.67 (s, O=$COCH_3$), 2.65–1.20 (complex multiplets, H-1, 2, 3, 4, 6, 7, 7′).

Alkylation of 3 with Iodomethane. A solution of **3** (1.83 g, 12.19 mmol) in THF (15 ml) was added dropwise to a solution of lithium iodode (1.82 g, 13.59 mmol) in iodomethane (10 ml) and THF (5 ml). The reaction mixture became turbid and warmed to ca. 45 °C. The reaction mixture was allowed to stir under nitrogen for 1 h at room temperature and was then concentrated under vacuum to a yellow slurry. The slurry was taken up in CH_2Cl_2, filtered through a fine porosity, sintered glass funnel (to remove LiI), dried ($MgSO_4$), and concentrated in vacuo to yield 2.62 g (74%) of crude 3-methyl-3-carbomethoxy-5-iodonortricyclene as a yellow oil which rapidly turned green upon exposure to light and air.

Purification of 6. A 1.98-g portion of the crude product was subjected to column chromatography on silica gel (50 g) with CH_2Cl_2, and 1.78 g of a yellow oil was obtained. A 0.48-g portion of the oil was subjected to preparative TLC (silica gel, CH_2Cl_2, fluoresceine indicator) which yielded 0.40 g of pure **6** as a pale yellow oil.

Anal. Calcd for $C_{10}H_{10}IO_2$: C, 41.09; H, 4.48. Found: C, 41.15; H, 4.49.

Spectroscopic Data for 6. Ir (neat) 3.40 (CH), 3.25 (sh, cyclopropyl CH), 5.79 (C=O), 12.15 μ (nortricyclene skeleton);[5a-c] near ir (CH_2Cl_2) λ_{max} 1.655 μ (ϵ 1.296);[6] NMR ($CDCl_3$) δ 3.92 (broad singlet, H-5), 3.68 (s, O=$COCH_3$), 1.23 (s, C–CH_3), 2.65–1.10 (complex multiplets, H-1, 2, 4, 6, 7, 7′).

Alkylation of 3 with Benzyl Iodide. A solution of **3** (1.02 g, 6.79 mmol) in THF (5 ml) was added dropwise to a solution of LiI (0.6 g, 4.5 mmol) and benzyl iodide (1.57 g, 7.2 mmol) in THF (10 ml). The reaction mixture was allowed to stir under nitrogen for 3 h at room temperature and was then concentrated in vacuo. The remaining slurry was treated with CH_2Cl_2 (10 ml) and extracted with three 25-ml portions of H_2O. The combined aqueous extracts were back extracted with three 25-ml portions of CH_2Cl_2. The organic solutions were combined, dried ($MgSO_4$), and concentrated and yielded 2.56 g of a thick yellow oil. A sample of analytically pure material was obtained by adsorption chromatography (column and preparative TLC).

Anal. Calcd for $C_{16}H_{17}IO_2$: C, 52.19; H, 4.65. Found: C, 52.03, 51.94; H, 4.67, 4.73.

Spectroscopic Data for 8. Ir (neat) 5.79 (C=O), 6.23 (C=C), 6.69 (C=C), 12.15 μ (nortricyclene skeleton);[5a-c] near ir (CH_2Cl_2) λ_{max} 1.656 μ (ϵ 1.155) (first CH stretching vibration overtone characteristic of nortricyclenes);[6] NMR ($CDCl_3$) δ 7.19 (m, 5 H), 3.90 (broad singlet, 1 H, H-5), 3.51 (s, 3 H, O=$COCH_3$), 2.85 (m, 2 H, –CH_2–), 2.5–1.2 (complex multiplets, 8 H).

Control: 3 and Iodomethane. A solution of **3** (0.254 g, 1.691 mmol) in THF (1.0 ml) was added to a solution of iodomethane (1.0 ml) in THF (1.0 ml). The reaction mixture was allowed to stir for 5 h at room temperature and was then concentrated in vacuo to 0.217 g of an oil identified by NMR analysis as unreacted 1-carbomethoxyquadricyclene (**3**).

Control: 3 and Benzyl Iodide. A solution of **3** (0.278 g, 1.85 mmol) in THF (1.0 ml) was added to a 2-ml solution of benzyl iodide (0.17 g, 0.78 mmol) in THF, and the resulting solution was allowed to stir for 5 h at room temperature in indirect light. The reaction mixture was then concentrated in vacuo and gave 0.370 g of an *oil*, determined by NMR analysis to be a 0.24:1.00 mol mixture of benzyl iodide and unreacted 1-carbomethoxyquadricyclene (**3**).

Reductive Deiodination of 6. A sample of crude **6** (2.73 g) was dissolved in methanol (20 ml) and heated in the presence of excess zinc dust for 4 days at 60 °C. The insoluble material was then removed by filtration, and the filtrate was concentrated at reduced pressure. The oil which remained was dissolved in ether (100 ml), washed with three 100-ml portions of dilute ammonium hydroxide, and reconcentrated to a light yellow oil (0.67 g). GLC analysis of the oil revealed at least eight components, the major component being 3-methyl-3-carbomethoxynortricyclene (**7**). A small quantity of **7** (0.049 g) was isolated by collection from the GLC column.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 72.26; H, 8.49. Found: C, 72.17; H, 8.37.

Spectroscopic Data for 7. Ir (neat) 3.42 (CH), 3.27 (*weak* sh, cyclopropyl CH), 5.75 (ester C=O), 12.41 μ (nortricyclene skeleton); NMR ($CDCl_3$, 60 MHz) δ 3.65 (s, O=$COCH_3$), 1.12 (s, C–CH_3), 2.5–0.7 (complex multiplets fused into C–CH_3 singlet at high end); NMR ($CDCl_3$, 300 MHz) δ 3.67 (s, O=$COCH_3$), 1.15 (s, C–CH_3), 1.27 (~8-line multiplet, 6 H), 1.47, 1.65 (pair of doublets, ~1:4 relative intensity, J ~ 2 Hz, 1 H), 1.93, 2.22, 2.41 (three singlets, ~4:1:1 relative intensity, 1 H).

Reductive Deiodination of 8. A sample of crude **8** (7.27 g) was dissolved in methanol (35 ml) and heated in the presence of zinc dust (2 g) for 24 h at 60 °C. The cooled mixture was then filtered, and 1.0 g of gray solid was removed. The filtrate was concentrated to a viscous yellow oil which was redissolved in methanol. The resulting solution was cooled, and an off-white solid (presumably ZnI_2) precipitated which was then removed by filtration (yield 0.87 g). This procedure was repeated until precipitation was no longer significant. The final crude oil was treated with water (20 ml) and extracted once with ether (30 ml). The ether solution was isolated,

dried, and concentrated and gave 2.10 g of a yellow oil, GLC analysis of which revealed at least 20 components, many of them minor. The major component (~30% relative peak area), 3-carbomethoxy-3-benzylnortricyclene (**9**), was collected in small quantity from the GLC column, and eventually it solidified (mp 38.0–39.5 °C). A sample of analytical purity was obtained by distillation of the crude product (~40 °C 0.05 mm) which yielded a white semisolid. The distilled material was vacuum pumped (room temperature, 0.05 mm) in a sublimator, and that semisolid which remained in the sublimator gave the correct CH analysis.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.43. Found: C, 79.01; H, 7.58.

Spectroscopic Data for 9. Ir (neat) 3.32 (sh, cyclopropyl CH), 3.44 (CH), 5.77 (C=O), 12.40 μ (nortricyclene skeleton); NMR ($CDCl_3$, 300 MHz) δ 1.07–1.43 (complex multiplet, 6 H), four sharp resonances at 1.85, 1.88, 2.05, 2.16 (2 H), 2.78 (AB quartet, $-CH_2-$ adjacent to an asymmetric center), 3.50 (s, $O{=}COCH_3$), 6.97–7.27 (complex aromatic multiplet, 5 H). Minor impurites were observed in the spectrum.

Registry No.—**3**, 24161-47-5; **4**, 57951-46-9; **6**, 57951-47-0; **7**, 57951-48-1; **8**, 57951-49-2; **9**, 57951-50-5; lithium iodide, 10377-51-2; iodomethane, 74-88-4; benzyl iodide, 620-05-3.

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Preparation of Aroylbenzoic Acid. Reaction of Aryllithium Reagents with Phthalic Anhydride[1]

William E. Parham* and R. M. Piccirilli

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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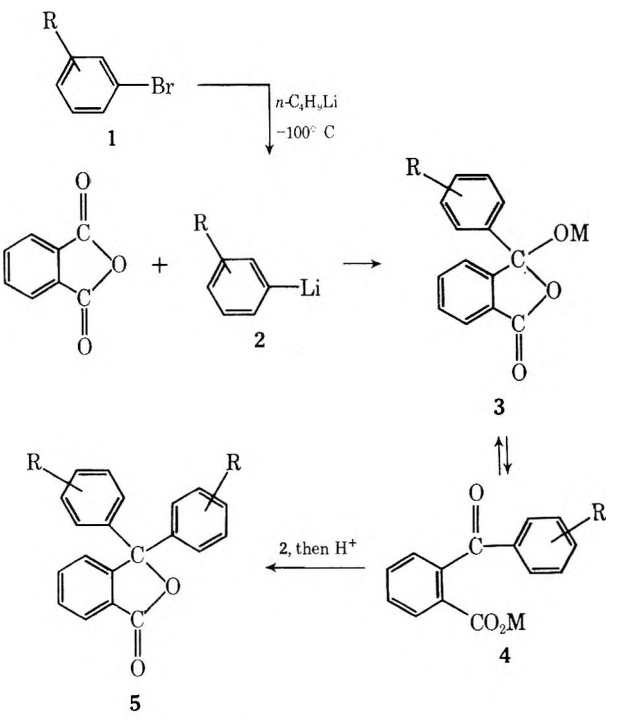
The preparation of a benzoylbenzoic acid by reaction of Grignard reagents with phthalic anhydride[2-4] offers advantages over the usual synthesis involving phthalic anhydride, aromatic hydrocarbons, and aluminum chloride in that isomers can be obviated when substituted aromatic compounds are employed. The method is limited, however, since Grignard reagents cannot be employed if the aromatic system contains functional groups that react with Grignard reagents. Since it has been shown[5-8] that organolithium reagents can be prepared at low temperature by halogen–metal exchange of aryl bromides substituted with groups normally reactive toward Grignard reagents (COO^-, CN, NO_2), the reaction of aryllithium reagents with phthalic anhydride has been examined as a route to *o*-benzoylbenzoic acids substituted with cyano functions. Previously, there has been little work related to the reaction of aryllithium with phthalic anhydride. Wittig and Leo report[9] that the reaction of phenyllithium with phthalic anhydride gives only a resinous compound and triphenylcarbinol, while Wilson reported an unworkable oil from which some diphenylphthalide[10] was isolated by distillation.

The reaction of organometallic reagents with phthalic anhydride is thought to proceed as shown in Scheme I. The products are generally *o*-benzoylbenzoic acids (**4**) and/or phthalides (**5**). Initially it was hoped that at low temperature, the equilibrium between the lithium salts **3** and **4** might favor **3**, which would obviate the necessity of employing inverse addition and/or an excess of phthalic anhydride to minimize phthalide (**5**) formation.[3] However, preliminary experiments using phenyllithium showed that this was not the case. When phthalic anhydride (1 equiv) was added to phenyllithium (1 equiv) at −78 °C the yield of phthalide **5a** was 78% base on phenyllithium. When the same ratios were maintained but the order of addition reversed, the yield of isolated phthalide **5a** was 9% while the yield of *o*-benzoylbenzoic acid was 35%. Furthermore, the yield of *o*-benzoylbenzoic acid was further increased (55%) when excess (2 equiv) of phthalic anhydride was employed.

Scheme I



a, R = H
b, R = OCH_3 (ortho)
c, R = CN (ortho)
d, R = CN (meta)
e, R = CN (para)
f, R = NO_2 (ortho)

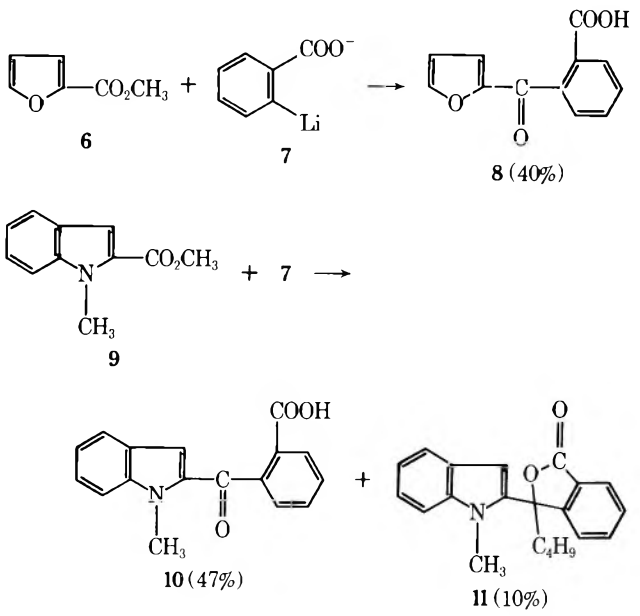
In subsequent experiments, the aryllithium reagent was added rapidly to 2 equiv of phthalic anhydride in tetrahydrofuran at −100 °C. Reasonably good yields of substituted benzoylbenzoic acids were obtained; the results are summarized in Table I.

Table I. Reactions of Aryllithium Derivatives with Phthalic Anhydride

Aryl halide	Product[f]	Yield, %	Mp, °C
o-$CH_3OC_6H_4Br$ (**1b**)	**4b** (M = H)	70	142–144[a]
o-NCC_6H_4Br (**1c**)	**4c** (M = H)	87	146–147[b]
m-NCC_6H_4Br (**1d**)	**4d** (M = H)	60	175–176[c]
p-NCC_6H_4Br (**1e**)	**4e** (M = H)	71	179–186[d]
o-$O_2NC_6H_4Br$ (**1f**)	**4f** (M = H)	43	174–176[e]

[a] Lit.[4] 145–146 °C from CH_3COOH. [b] From H_2O. [c] From ethanol. [d] From ethanol–water. [e] From $CHCl_3$. [f] Satisfactory analytical data (±0.3% for C, H, N) for all new compounds were submitted for review.

Scheme II



Incidental to this study certain heterocyclic analogues of *o*-benzoylbenzoic acid were conveniently prepared by adaptation of the method previously described[7] for benzoylbenzoic acid as shown in Scheme II.[11]

The combination of these two methods provides considerable flexibility for the synthesis of o-aroylbenzoic acids not easily available by other routes.

Experimental Section

General Procedure. Aryllithium derivatives **2** were prepared from the corresponding aryl halides **1** (0.02 mol) in tetrahydrofuran (80 ml distilled from $LiAlH_4$) with *n*-butyllithium (9 ml of 2.3 M solution in hexane, 0.02 mol) at −100 °C as previously described[6,7] and were added (pumped by nitrogen pressure) as rapidly as possible to a solution of phthalic anhydride (0.04 mol) in 125 ml of dry tetrahydrofuran at −100 °C. The mixture was maintained at −100 °C for 1 h and then allowed to warm to room temperature. Tetrahydrofuran was removed (in vacuo) and the solid residue shaken with a mixture of ether (60 ml) and water (100 ml). The aqueous solution was made acidic with hydrochloric acid and was extracted with ether. The ether was extracted with saturated sodium bicarbonate to remove acid. Phthalides **5** were obtained from the ether layer. The alkaline extract was acidified and the solid was collected and recrystallized as described in Table I.

2-(2-Furoyl)benzoic acid (8) was prepared from lithium *o*-lithiobenzoate (from 0.05 mol of o-bromobenzoic acid) as described[6] and 2-methylfuroate. After warming the mixture to room temperature, the tetrahydrofuran was removed in vacuo and water (250 ml) was added to the residue. The aqueous solution was washed with ether, acidified with hydrochloric acid, and extracted with ether (3 × 30 ml). The dried ($MgSO_4$) ether extracts were evaporated in vacuo to give the crude acid as an oil which crystallized when treated with ethyl acetate followed by evaporation of all solvent (5.5 g, 52% yield, mp 150–153 °C, mp 154–156 °C from ethyl acetate); νC=O 1660, 1700 cm^{-1}.

Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.50; H, 3.95.

2-(1-Methyl-2-indoloyl)benzoic acid (10) was prepared from methyl 1-methylindole-2-carboxylate (0.03 mol) essentially as described for 8. Tetrahydrofuran was removed from the crude reaction mixture in vacuo and water (250 ml) was added to the residue. The resulting mixture was extracted with ether. From the ether extract there was obtained 0.38 g (7%) of starting ester. The mixture of acids obtained by acidification of the alkaline layer was collected (ether extraction) and recrystallized from benzene to give 4.00 g (47% yield) of pure 2-(1-methyl-2-indoloyl)benzoic acid (**10**), mp 164–165 °C.

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.01. Found: C, 72.97; H, 4.62; N, 4.91.

Evaporation of the benzene from which **10** was crystallized gave a semisolid to which some cold ether was added. The resulting solid was collected and recrystallized from ethyl acetate to give 0.88 g (mp 131–132 °C 10% yield) of lactone **11**.

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.96; H, 6.62; N, 4.38. Found: C, 78.93; H, 6.50; N, 4.34.

Registry No.—**1b**, 578-57-4; **1c**, 2042-37-7; **1d**, 6952-59-6; **1e**, 623-00-7; **1f**, 577-19-5; **4b**, 1151-04-8; **4c**, 57901-51-6; **4d**, 57901-52-7; **4e**, 20643-60-1; **4f**, 57901-53-8; **6**, 611-13-2; **8**, 57901-54-9; **9**, 37493-34-8; **10**, 57901-55-0; **11**, 57901-56-1; phthalic anhydride, 85-44-9; lithium *o*-lithiobenzoate, 57901-57-2.

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Side Reactions in Peptide Synthesis. III.[1] Intermolecular Acylation by an Unprotected Side Chain Carboxyl Group[2]

Sesha Natarajan and Miklos Bodanszky*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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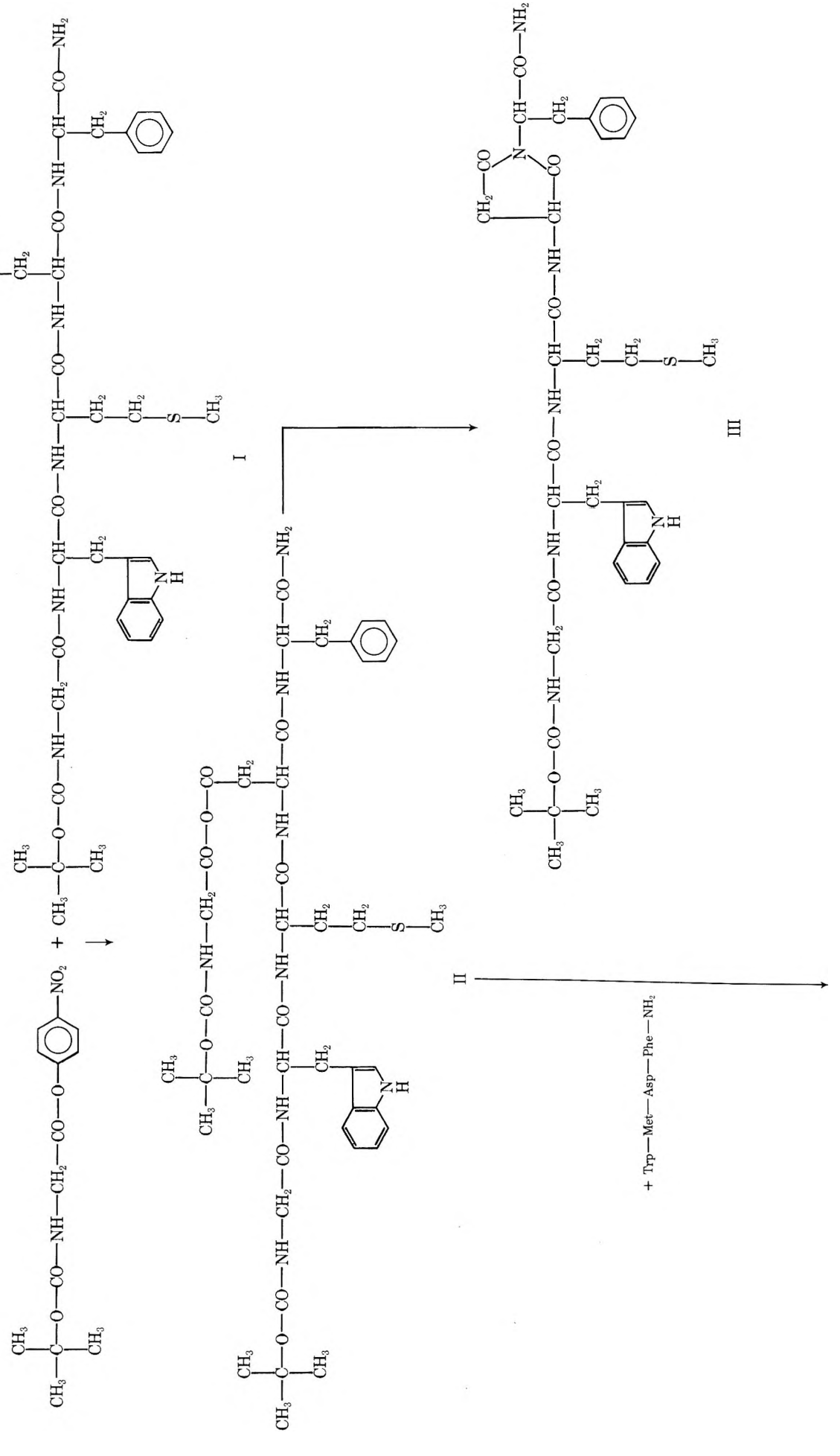
In a recent communication[1] we reported a side reaction in the preparation of the pentapeptide derivative *tert*-butyloxycarbonylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalaninamide (I, Chart I), an intermediate in the syntheses of gastrin,[3] cholecystokinin[1], and caerulein.[4] The conditions of the reaction suggested the mixed anhydride II as the reactive intermediate leading—through *intramolecular* acylation—to the by-product III, a succinimide derivative. Our conclusion that the unprotected carboxyl of the aspartyl residue can compete with the amino group in the nucleophilic attack on an active ester, particularly when the latter is present in excess, is now further supported by the isolation of a second by-product.

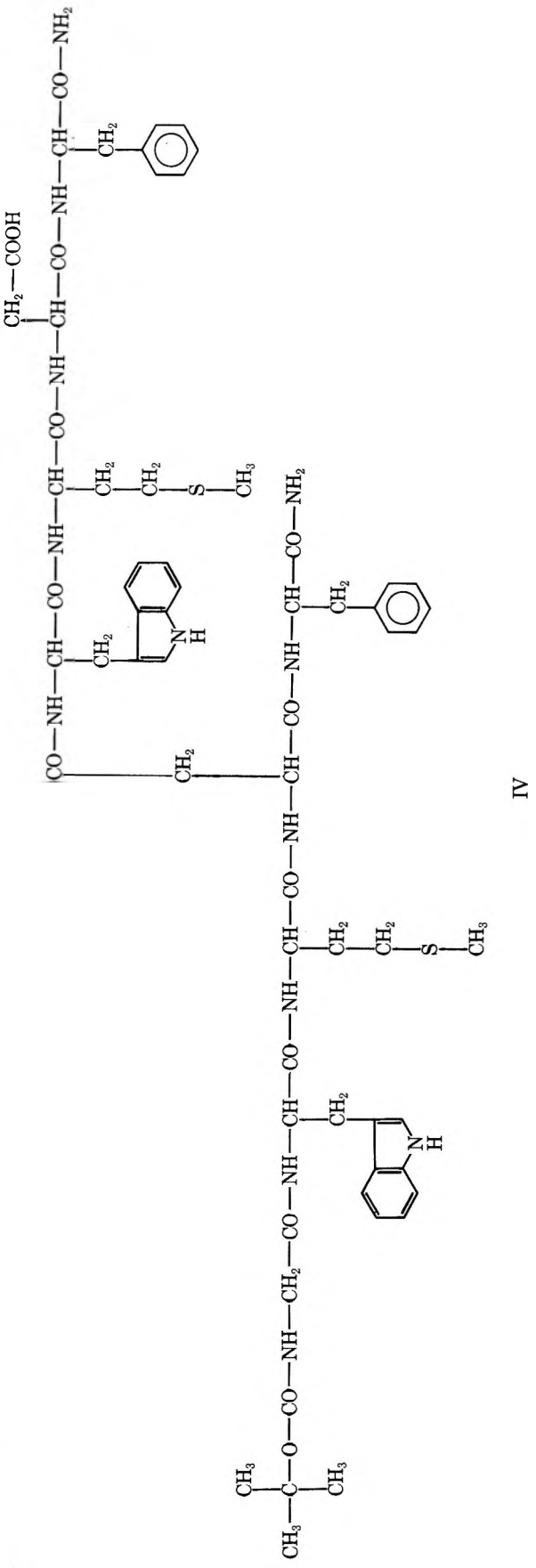
During recrystallization of samples of compound I from 95% ethanol, small amounts of a crystalline material, insoluble even in the hot solvent, were obtained. Amino acid analysis of this new by-product revealed the amino acid constituents of I, but in the molar ratio Asp 2, Gly 1, Met 2, Phe 2, Trp 2. This immediately suggested that the nonapeptide derivative IV was in hand, formed via the same mixed anhydride (II)[5] but in an *intermolecular* reaction with the amino component, a tetrapeptide amide (as shown in Chart I).

The structure proposed for compound IV was supported by its degradation (after deblocking) with cyanogen bromide[6] and with aminopeptidase M[7] (Chart II).

The unexpected[8] formation of a nonapeptide derivative (IV) during the preparation of a blocked pentapeptide (I) suggests that the protection of carboxyl groups has to be

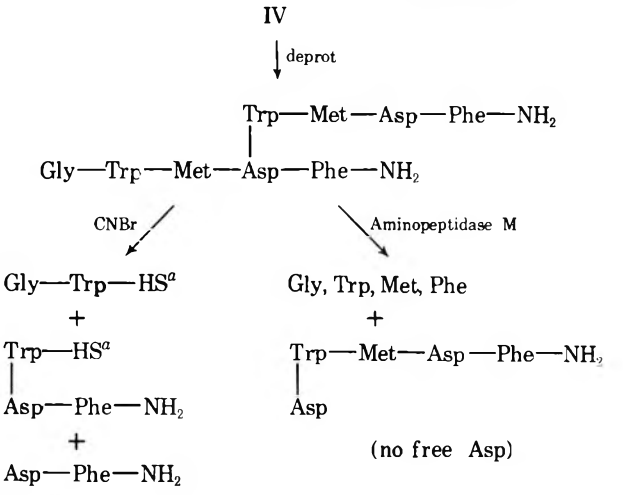
Chart I. Formation of the Nonapeptide Derivative IV





IV

Chart II. Degradation of the Nonapeptide IV



[a] HS designates both homoserine and its lactone.

considered in reactions that involve acylation with active esters.

Experimental Section

On thin layer plates of silica gel, peptides were detected by Ehrlich reagent, ninhydrin spray, and by uv. For development, the solvent system ethyl acetate–pyridine–acetic acid–water (60:20:6:11) was applied. Reagent-grade solvents were used. Amino acid analyses were carried out by the Spackman–Stein–Moore method[9] after hydrolysis with 6 N HCl at 110 °C for 16 h, unless otherwise stated.

Isolation of Compound IV. A suspension of crude protected pentapeptide amide[1] (I, 0.61 g) in 95% ethanol (15 ml) was heated on a steam bath. A small portion of the material remained undissolved and was collected by centrifugation. The solid was extracted three times with hot 95% ethanol (20 ml each). It was dissolved in dimethyl sulfoxide (1.5 ml), the solution centrifuged to remove mechanical impurities, and the solvent removed in vacuo. The residue was triturated with 95% ethanol (1 ml), centrifuged, and dried. The purified material IV (15 mg) had mp 235–237 °C, R_f 0.37. Amino acid analysis: Asp, 2.0; Gly, 1.0; Met, 2.1; Phe, 2.0; Trp (from uv), 1.9. The product gave positive reaction with Ehrlich reagent and negative reaction with ninhydrin.

Degradation of (Deblocked) Compound IV with Cyanogen Bromide. Compound IV (12 mg) was dissolved in 70% formic acid (1 ml) and kept at room temperature for 3 h. The solution was evaporated to dryness in vacuo and the deprotected peptide dissolved in 70% formic acid (1.5 ml). Cyanogen bromide (150 mg) was added and the solution stirred at room temperature for 20 h. Water (8.5 ml) was added and the solution was lyophilized. A preparative TLC on silica gel (20 × 20 cm plate) was carried out; the plate was developed four times. The bands were located by uv fluorescence. The major bands were eluted with the solvent system used for TLC (5 ml) and then with ethanol (95%, 5 ml). The solutions were concentrated and hydrolyzed for amino acid analysis. Band I (R_f 0.47): Asp, 0.8; homoserine, 0.5; Phe, 1.0; homoserine lactone, 0.4; Trp (mostly dec), trace. Band II (R_f 0.42): homoserine, 0.4; Gly, 1.0; homoserine lactone, 0.4; Trp (mostly dec), 0.1. Band III (R_f 0.19): Asp, 1.0; Phe, 0.9.

Hydrolysis of Deblocked IV with Aminopeptidase M. Compound IV (1.5 mg) was deblocked with trifluoroacetic acid (0.1 ml containing 5% anisole) at 0 °C for 30 min. The acid was removed and the residue triturated with ether. To the solid product was added 0.1 M Tris–HCl buffer (pH 7.7, 1 ml), followed by aminopeptidase M (Röhm, ca. 1000 milliunits). Toluene (4 drops) was added and the solution was incubated at 37–38 °C for 72 h. The reaction was arrested by heating the solution on a steam bath for 5 min. The solution was evaporated with a stream of nitrogen and citrate buffer (pH 2.2, 5 ml) was added. The soluble portion was separated by centrifugation and subjected to amino acid analysis: Gly, 1.0; Met, 1.0; Phe, 1.0; Trp, 0.9.

Registry No.—I, 5915-71-9; IV, 57821-06-4.

References and Notes

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Reaction of Phosphoranes with Formate Esters. A New Method for Synthesis of Vinyl Ethers[1]

Vinayakam Subramanyam,* Eileen H. Silver, and Albert H. Soloway

Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115

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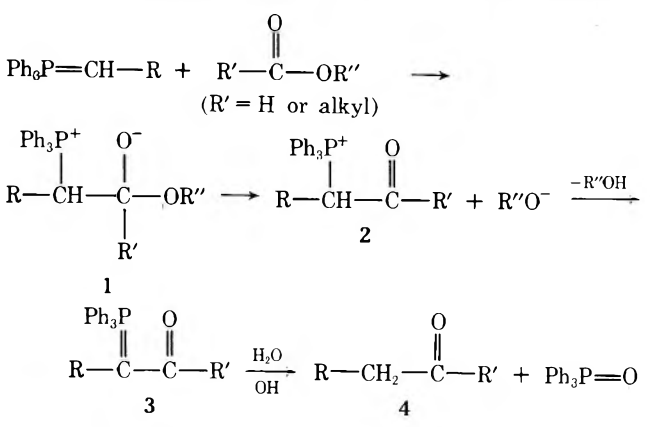
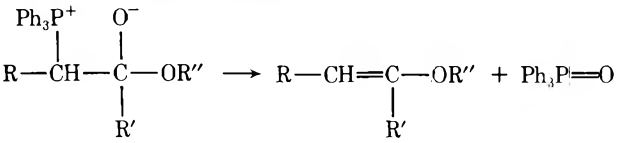
The Wittig reaction between phosphorus ylides and esters of carboxylic acids initially give β-ketoalkylphosphonium salts (**2**), which eliminate R″OH to form the stabilized β-ketoalkylidene phosphoranes (**3**).[2,4] Hydrolytic cleavage of these provides a useful synthesis of corresponding carbonyl compounds (**4**). Ethyl formate is reported to give aldehydes.[3] A reinvestigation of the reaction with formate esters was undertaken with the hope of developing a general method for the synthesis of substituted vinyl ethers instead of the reported aldehydes.[3] This study demonstrates the general feasibility for preparing vinyl ethers by this sequence.

Earlier investigations[2-5] of the mechanism of these acylation reactions indicate an initial nucleophilic attack by the ylide on the carbonyl function to form a betaine (**1**) intermediate. Elimination of OR″ from **1** as alkoxyl ion generates the phosphonium salt **2**. If such elimination is precluded, an alternative course of reaction is elimination of $Ph_3P{=}O$ to form vinyl ether **5**.



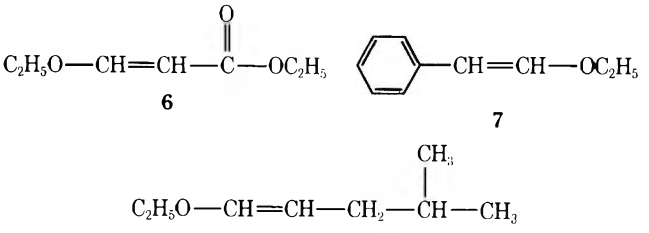


1 **5**

The latter possibility prompted us to explore the role, if any, of the group R′ of the ester function in determining the course of reaction. The reactions were carried out with phosphoranes ($Ph_3P{=}CHR$) that were stabilized (R = CO_2Et), partially stabilized (R = Ph), or reactive (R = alkyl or OCH_3). The esters used were those of formic, acetic, butyric, and benzoic acids and primary, secondary, and tertiary alcohols.

In reactions of phosphoranes with formate esters, where R′ is hydrogen, elimination of $Ph_3P{=}O$ occurred with the formation of vinyl ethers. Reaction conditions and yields depended upon the reactivity of the ylides.

The stable ylide carbethoxymethylenetriphenylphosphorane on refluxing with ethyl formate gave the vinyl ether **6** in 95% yield. A partially stabilized ylide derived from benzyltriphenylphosphonium chloride reacts with ethyl formate at room temperature to give **7** in 90% yield. However, reactive phosphoranes derived from 3-methylbutyltriphenylphosphonium bromide and methoxymethyltriphenylphosphonium chloride react with ethyl formate at room temperature to yield the reported β-formylalkylidene phosphorane.[4] When these reactions were carried out at −78 °C, the 3-methylbutylidenephosphorane gave 22% yield of vinyl ether **8**, but no vinyl ether was obtained from methoxymethylenetriphenylphosphorane at this temperature.

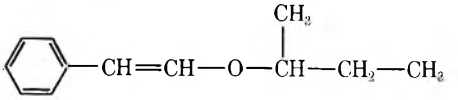


6 **7**

8

It appears that in reactive phosphoranes elimination of alkoxyl ion is favored at room temperature. This tendency is reduced at −78 °C and as a result some vinyl ether is formed. In the case of methoxymethylenetriphenylphosphorane, elimination of alkoxyl ion seems to be the only preferred mode of reaction, even at −78 °C. Consequently, no vinyl diether is formed.

In a second set of experiments, the partially stabilized ylide benzylidenetriphenylphosphorane was allowed to react with formate esters of *sec*-butyl alcohol and cyclohexanol. The red color characteristic of the phosphorane still remained after 8 h at 50 °C, but on work-up the corresponding vinyl ethers **9** and **10** were obtained in yields of 24



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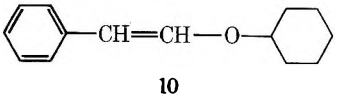

10

and 27%, respectively. A fourfold excess of formate esters and longer reaction times did not improve the yield. When

reactions are carried out for longer periods than 8 h, *trans*-stilbene is formed in appreciable amounts possibly through dimerization of carbene intermediates. Similar results have been reported.[7] The low yields may be attributed in part to steric hindrance of bulky *sec*-alkyl groups. *tert*-Butyl formate, for example, does not react with any of the phosphoranes mentioned.

Our attempts to obtain vinyl ethers from the reaction of stabilized ylides as well as benzylidenetriphenylphosphorane with esters of acetic, butyric, and benzoic acids proved to be unsuccessful under a variety of conditions of temperature and reaction medium. Reactive ylides have been reported to give β-ketoalkylidenephosphoranes.[8]

In all cases, the products are mixtures of cis and trans isomers but the proportions vary depending upon the nature of the ylide. The stable ylide carbethoxymethylenetriphenylphosphorane gave cis and trans vinyl ethers in a 10:90 ratio, while with benzylidenephosphorane the proportion of cis isomer increased to 22% of the product. A cis–trans ratio of 45:55 was observed with the reactive ylide 3-methylbutylidenetriphenylphosphorane. The ratios were based on the vinylic absorptions in the NMR spectra of products.

It appears that substituted vinyl ethers may be conveniently synthesized by reaction of phosphoranes with ethyl formate under suitable conditions, thereby providing a general method for the conversion of alkyl and aralkyl halides to vinyl ethers.

Experimental Section

NMR spectra were recorded on a Varian T-60 instrument in $CDCl_3$. Chemical shifts are reported in δ units from internal Me_4Si, and are followed by parentheses giving multiplicity of signal, coupling constant if applicable, and number of protons. Spin multiplicity is given by s = singlet, d = doublet, t = triplet, q = quartet. All compounds showed satisfactory analytical data (±0.4% for C and H). Boiling points are uncorrected.

2-Carbethoxyethenyl Ethyl Ether (6). Carbethoxymethylenetriphenylphosphorane was prepared according to the published procedure.[9] A mixture of 17.5 g (0.05 mol) of the phosphorane and 40 ml of ethyl formate was heated under reflux for 4 h. The reaction mixture was cooled in ice and the triphenylphosphine oxide formed was separated by filtration. Excess ethyl formate was removed by distillation at atmospheric pressure. Distillation of the residual liquid at 0.5 Torr gave 6.8 g (95% yield) of a pleasant-smelling liquid boiling at 60–61 °C.

NMR spectrum: δ_{Me_4Si} 1.25 and 1.33 (t, t, 3 H, 3 H, $-CH_3$ of the two ethyl groups), 3.9 and 4.1 (q, q, 2 H, 2 H, $-CH_2-$ of the two Et), 4.78 and 5.17 (d, d, J = 7 and 13 Hz, together 1 H, =CHOEt), 6.57 and 7.57 (d, d, J = 7 and 13 Hz, together 1 H, $=CHCO_2Et$).

Ethyl Styryl Ether (7). Benzylidenetriphenylphosphorane was generated, according to the method of Corey et al.,[10] from 39.0 g (0.1 mol) of benzyltriphenylphosphonium chloride and 2.6 g (0.11 mol) of sodium hydride in 400 ml of dimethyl sulfoxide. Ethyl formate (15 g, 0.2 mol) was added to the phosphorane and stirred at room temperature for 3 h, during which the red color gradually changed to pale brown. The reaction mixture was thrown into 800 ml of water, the mixture was extracted exhaustively with pentane, and the combined pentane extract was dried over anhydrous $MgSO_4$. Pentane was distilled off under reduced pressure. A clear, colorless liquid boiling at 63 °C (1 mmHg) was obtained in 90% yield (13.3 g).

NMR spectrum: δ_{Me_4Si} 1.25 (t, 3 H, CH_3 of Et), 3.75 (q, 2 H, $-CH_2-$ of Et), 5.18 and 5.8 (d, d, J = 7 and 13 Hz, together 1 H, =CHOEt), 6.1 and 6.93 (d, d, J = 7 and 13 Hz, together 1 H, $=CHC_6H_5$), 7.08 (broad s, 5 H, C_6H_5-).

4-Methyl-1-pentenyl Ethyl Ether (8). A suspension of 20.7 g (0.05 mol) of 3-methylbutyltriphenylphosphonium bromide in 250 ml of anhydrous ether was stirred with 21 ml of a 2.4 M solution of *n*-butyllithium (0.05 mol) at room temperature in an atmosphere of N_2. After 0.5 h it was cooled in a bath of dry ice–acetone for 10 min. A solution of 4.1 g (0.055 mol) of ethyl formate in 10 ml of ether was slowly added with stirring. The red color discharged slowly. The reaction mixture was allowed to warm to room temperature. About 10 ml of alcohol was added and the slurry filtered. The filtrate was washed with water, dried with $MgSO_4$, and solvent removed by distillation at atmospheric pressure. The residue was distilled from a small flask and 1.4 g (22% yield) of compound 8 was obtained as a colorless liquid boiling at 132–133° (760 mm).

NMR spectrum: δ_{Me_4Si} 0.9 [d, 6 H, methyls of $-CH(CH_3)_2$], 1.23 (t, 3 H, $-CH_3$ of OEt), 1.73 and 1.85 (m, m, together 3 H, –CH– and $-CH_2-$ of C-4 and C-3 respectively), 3.66 and 3.73 (q, q, together 2 H, $-CH_2-$ of OEt, trans and cis isomers, respectively), 4.27, 4.37, 4.60, and 4.82 (t, t, t, t, together 1 H, J = 7 and 13 Hz, respectively, $=CHCH_2$ cis and trans), 5.93, 6.17 (d, d, together 1 H, J = 7 and 13 Hz, respectively, –CH= of EtOCH=).

***sec*-Butyl styryl ether (9) and cyclohexyl styryl ether (10)** were prepared by the same procedure used for making compound 7 from 0.05 mol of the benzylidenetriphenylphosphorane and obtained in 24 and 27% yields, respectively.

Registry No.—(*E*)-**6**, 5941-55-9; (*Z*)-**6**, 40648-44-0; (*E*)-**7**, 20565-86-0; (*Z*)-**7**, 13294-31-0; (*E*)-**8**, 16969-14-5; (*Z*)-**8**, 16969-29-2; (*E*)-**9**, 57967-99-4; (*Z*)-**9**, 14371-22-3; (*E*)-**10**, 57901-31-2; (*Z*)-**10**, 57901-32-3; carbethoxymethylenetriphenylphosphorane, 1099-45-2; ethyl formate, 109-94-4; benzylidenetriphenylphosphorane, 16721-45-2; 3-methylbutyltriphenylphosphonium bromide, 28322-40-9.

References and Notes

(1) This research was supported in part by a grant from the Navy, NR 108-979.
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Europium Shift Reagents. The Assignment of Aryl Stereochemistry in 6,6-Diarylbicyclo[3.1.0]hexan-3-*exo*-ols

David S. Crumrine* and Hui-Hsien Bert Yen

Chemistry Department, Loyola University of Chicago, Chicago, Illinois 60626

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As part of our studies on remote electronic interactions, we have studied the stereoselectivity of cylopropanation by substituted diarylcarbenoids.[1] The assignment of endo/exo aryl stereochemistry on the isomeric 6-phenyl-6-arylbicyclo[3.1.0]hex-2-ene products was a tremendous problem that could not be solved by uv spectroscopy,[2] ^{13}C NMR,[2] or OH-π bonding studies[3] on alcohol derivatives. CNDO calculations indicated that photoelectron spectroscopy would not be helpful.[2] Although ^1H NMR has been used to study the stereochemistry of various 6,6-disubstituted bicyclo[3.1.0]hexane derivatives[4] and a great number of phenylcyclopropanes,[5] the small (ca. 0.1 ppm) but regular shifts of the center of each aryl pattern seen here were not definitive. Europium shift reagents have been applied to a variety of stereochemical problems[6] and the necessary alcohol derivatives could be readily prepared[3] via hydroboration of the bicyclic olefins (eq 1). We therefore present a europium shift reagent study that clearly defines the aryl stereochemistry in 6,6-diarylbicyclo[3.1.0]hexan-3-*exo*-ols (3) and suggests the principal conformation of the 5 ring. We

Table I. Observed and Calculated Induced Shift Ratios in 6-Aryl-6-phenylbicyclo[3.1.0]hexan-3-*exo*-ols

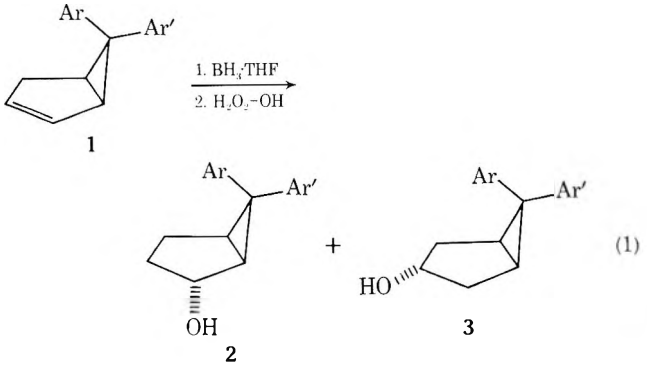
Proton[a]	Calcd[b]	PhPh (1.35/1)[c]	*p*-Br_{endo} (1.5/1)	*p*-Br_{exo} (1.63/1)	*p*-CN_{exo} (1.45/1)	*p*-Me_{endo} (0.85/1)	*p*-MeO_{endo} (1.5/1)[f]
H_{ac}	12.8	5.25	4.90	5.10	5.48	5.16	5.19
H_{at}	7.47	3.56	3.26	3.43	3.71	3.48	3.30
H_{cp}	5.77	2.24	1.93	2.02	2.40	2.05	2.13
H_{no}	2.52	0.368	0.324	0.306	0.377	0.320	0.314
H_{xo}	2.28	0.260	0.226	0.158	0.332	0.212	0.206
H_{nm}	1.07	0.143[d]	0.125	0.101	0.154	0.098	0.132
H_{xm}	1.16	0.150[d]	0.125	0.164	0.228	0.319	0.103
Corr coeff		0.988	0.989	0.987	0.988[e]	0.986	0.991

[a] See designations in Figure 2. [b] $10^3(3\cos^2\theta - 1)/R^3$. [c] Mole ratio of $Eu(fod)_3$ to substrate from which extrapolation to 1/1 was made following ref 13. [d] Assignment is uncertain since both rings have a para hydrogen. [e] If H_{np} is included, the correlation coefficient is still 0.988. [f] For the methoxy protons 0.061.

will also discuss the origin and interpretation of the aryl absorption patterns in the spectra before shift reagent was added.

Results and Discussion

The bicyclic olefins **1a–f** were prepared by zinc chloride catalyzed cyclopropanation of cyclopentadiene with the corresponding diaryldiazomethane.[7] The pure bicyclic olefins **1a–f** were individually hydroborated to give a mixture



	a	b	c	d	e	f
Ar	Ph	Ph	Ph	*p*-BrC_6H_4	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$
Ar'	Ph	*p*-CNC_6H_4	*p*-BrC_6H_4	Ph	Ph	Ph

of the corresponding 6,6-diarylbicyclo[3.1.0]hexan-*exo*-2-ols **2** and 6,6-diarylbicyclo[3.1.0]hexan-*exo*-3-ols **3** which were chromatographically separated. The exo hydroxyl stereochemistry was confirmed for the 2-ols by comparison to the bromo cases where both *endo*-2-ols and *exo*-2-ols are known[3] and for the 3-alcohols by comparison to the diphenyl case where both isomers are known.[3,8] In both cases the endo methine on the carbon bearing the exo hydroxyl has a ^1H NMR absorption at higher field than the exo methine on the other isomer as one would expect since the endo methine can be shielded by both the cyclopropyl ring[9] and the endo phenyl ring.[10]

The aryl region of the unshifted spectra was interesting enough that we attempted to assign stereochemistry on the basis of the relative shift of the center of the aryl patterns following Closs' comment on the phenyl absorption of the *syn*- and *anti*-7-phenylbicyclo[4.1.0]heptanes.[5b] For simple geminal diphenyl cases, the lower phenyl pseudosinglet can be attributed to the endo phenyl moiety. The origin of this shift difference is interesting. Since it is essentially unchanged by different substituents in the 5 ring such as a double bond, a carbonyl at C-2 or C-3, or hydroxyls at C-2 or C-3, it probably originates from the exo phenyl group spending part of its time in a bisected conformation which has maximum overlap with the cyclopropyl ring. In this conformation the cyclopropyl ring shields[9] the ortho protons and causes an overall upfield shift for the exo aryl pattern.[5] However, the shift reagent work demonstrated that,

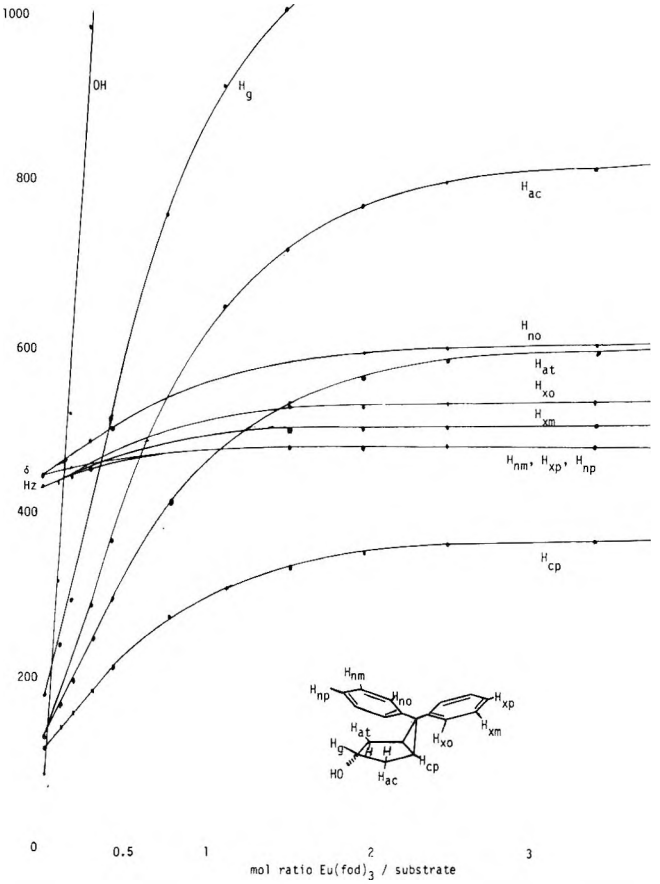


Figure 1. Europium induced shifts for 6,6-diphenylbicyclo-[3.1.0]hexan-3-*exo*-ol.

for substituted cases, such interpretations were frequently false since electron-donating substituents tend to raise and electron-withdrawing substituents tend to lower the average aryl chemical shift.[10] These substituent shifts are sufficient to void any simple interpretation.

The $Eu(fod)_3$[11] studies on the *exo*-3-ols **3a–f** were run in deuteriochloroform solution. Spectra were recorded after each addition and shifts were plotted vs. mole ratio of shift reagent to substrate (see Figure 1 for a sample plot of the diphenyl data for **3a**). Signal assignments depended on integration, signal multiplicity, and careful following of each signal as increments of shift reagent were added. The aliphatic protons H_g, H_{ac}, H_{at}, and H_{cp} were easily assigned. In each case, two aromatic doublet patterns with ca. 8 Hz ortho coupling moved measurably faster than the rest of the aromatic signals. If the pattern showed no further coupling it was assigned to the protons ortho to the cyclopropyl ring on a para-substituted phenyl ring, and if a ca. 2 Hz meta coupling was visible it was assigned to the protons ortho to the cyclopropyl ring on an unsubstituted phenyl

ring. The faster moving aromatic doublet was assigned to the endo phenyl ring (H_{no}), and the slower moving doublet was assigned to the exo phenyl ring (H_{xo}) in agreement with predictions of both the crude distance ($1/R^2$) as well as the more exact McConnell treatments.[6,12]

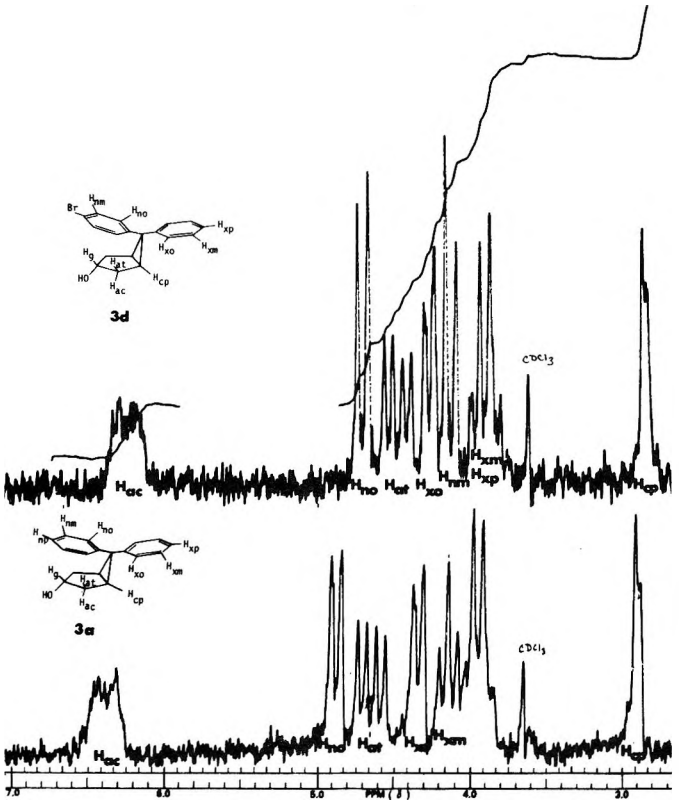


Figure 2. Portions of the shifted spectra for **3a** and **3d** (1000-Hz sweepwidth).

At ca. 1.4:1 mole ratio the lower field ortho doublet showed no meta coupling and the higher field doublet showed coupling allowing assignment of *endo-p*-bromophenyl **3d**, *endo-p*-methylphenyl **3e**, and *endo-p*-methoxylphenyl **3f** stereochemistry in these cases (for an example see Figure 2.) At similar mole ratios, the high-field doublet was clean but the lower field doublet showed a ca. 2 Hz meta coupling allowing assignment of endo phenyl stereochemistry in **3b** and **3c**. As shown in Figure 2, the diphenyl case **3a** showed meta coupling in both doublets. This analysis is consistent with the observation of marked changes in the aromatic signals assigned to the endo aryl group during the first few additions of shift reagent. The greater shifts induced in the endo ortho protons are first noticed as changes in apparent line width of the endo aryl signals when little or no change is seen in the line width of the exo aryl signals.

The observed values of $\Delta\nu_i/\nu$ are collected in Table I and were compared to McConnell calculations[12] on a variety of 1/1 molecular arrangements.[13] Positioning the europium ion was aided by the clear order $\Delta\nu_i/\nu = H_{ac} > H_{at} > H_{cp}$ for the aliphatic protons, as well as the small positive shifts observed for the *endo-p*-methyl and *endo-p*-methoxyl absorptions in **3e** and **3f**. This small but nearly linear shift of the methoxyl protons even at 1.48/1 mole ratio rules out any second site complexation occurring here in preference to the hydroxyl oxygen. This order is reproduced only for the conformation shown in Figure 3 where the 5 ring has a shallow chair conformation with 10–12° of pucker and the europium is located 3 Å from the oxygen with the Eu–O

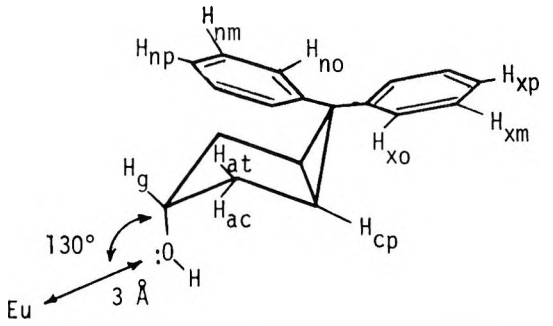


Figure 3. Best molecular arrangement for europium–substrate complexation.

axis at 130° to the C–O bond.[14] The observed relative induced shifts $\delta\nu_i/\nu$ for each of the 3-ols are collected in Table I along with the calculated values using this conformation and the correlation coefficients.

The hydroxyl protons and H_g were not included in the correlation since they are known to correlate poorly because of their closeness to the europium ion.[15] Only in the *exo-p*-cyanophenyl case **3b** was a para proton sufficiently resolved to allow assignment. The overall order of induced shifts is calculated to be $H_{ac} > H_{at} > H_{cp} > H_{no} > H_{xo} > H_{xm} > H_{nm} > H_{xp} > H_{np}$, but small changes in conformation can change the order among the meta and para protons. The experimental values seem to reflect this sensitivity. For acyclic unsubstituted phenyl systems[16] the order of induced shifts is $H_o > H_m > H_p$ in agreement with our work, but for benzo systems interpretation[17] is more difficult.

Experimental Section

All melting points were determined on a hot stage apparatus and are corrected. The ir spectra were determined on a Beckman Acculab 1 or Perkin-Elmer 700. NMR spectra were recorded on a Varian A-60A using tetramethylsilane as internal standard and deuteriochloroform solvent. Aldrich BH_3·THF and $Eu(fod)_3$ from Kary Laboratories were used as received. The diarylbicyclic olefins **1a–f** were prepared by zinc chloride catalyzed cyclopropanation of cyclopentadiene with the corresponding diaryldiazomethane.[18] Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Hydroboration of the 6-Phenyl-6-arylbicyclo[3.1.0]hex-2-enes. The olefins were dissolved in dry THF and hydroborated with commercial BH_3·THF solution.[3] The best yields involved use of a 1/1.5 mole ratio instead of 1/0.33. Some of the 3-ol often crystallized out when the reaction mixture was poured into water before ether extraction. The remainder of the reaction mixture was then chromatographed on a slurry packed column of deactivated silica gel using 50% ether–hexane eluent. The 3-ol eluted first and was recrystallized and characterized. The later fractions containing the 2-ol were saved for later work. The product ratio by HPLC analysis was about 1.3:1 favoring the 3-ol and showing little substituent effect. Individual details and characterizations follow.

Hydroboration of 6,6-diphenylbicyclo[3.1.0]hex-2-ene, mp 80–81 °C (lit.[3] mp 79–80 °C), gave a quantitative yield of the 2- and 3-ols; 6,6-diphenylbicyclo[3.1.0]hexan-3-ol, mp 156–157 °C (lit.[3] 157–158 °C), was isolated.

Hydroboration of 6-*endo*-phenyl-6-*exo*-*p*-cyanophenylbicyclo-[3.1.0]hex-2-ene, mp 95–96 °C, gave a quantitative yield of the 2- and 3-ols; 6-*endo*-phenyl-6-*exo*-*p*-cyanophenylbicyclo-[3.1.0]hexan-3-ol, mp 70 °C, was isolated with NMR ($CDCl_3$) δ 7.55–6.85 (9 H Ar m with Ph peak at 7.28), 2.88 (1 H t, J = 7 Hz, HCOH), 2.65–1.62 (6 H m, CH_2 and cyclopropyl H), 1.47 (1 H s, OH); ir (mull) 3340 (OH), 3060, 3030, 2240 (CN), 1600, 1500, 1490, 1460, 1360, 1280, 1180, 1070, 1040, 960, 800, 780, 750, 720, 700 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.23; N, 5.09. Found: C, 82.96; H, 6.46; N, 4.97.

Hydroboration of 6-*endo*-*p*-bromophenyl-6-*exo*-phenylbicyclo-[3.1.0]hex-2-ene, mp 104–105 °C (lit.[3] mp 105–106 °C), gave a quantitative yield of the 2- and 3-ols; 6-*endo*-*p*-bromophenyl-6-

exo-phenylbicyclo[3.1.0]hexan-3-ol, mp 185–186 °C (lit.[3] 185.5–186.5 °C) was isolated.

The mother liquors obtained after extensive crystallization of the other isomers were rechromatographed and the fractions which were shown by NMR to be largely 6-*endo*-phenyl-6-*exo*-*p*-bromophenylbicyclo[3.1.0]hex-2-ene were then hydroborated to give a quantitative yield of the 2- and 3-ols; 6-*endo*-phenyl-6-*exo*-*p*-bromophenylbicyclo[3.1.0]hexan-3-ol, mp 83–85 °C (lit.[3] mp 87–88 °C), was isolated.

Hydroboration of 6-*endo*-*p*-methylphenyl-6-*exo*-phenylbicyclo-[3.1.0]hex-2-ene, mp 59–61 °C, gave a quantitative yield of the 2- and 3-ols; 6-*endo*-*p*-methylphenyl-6-*exo*-phenylbicyclo-[3.1.0]hexan-3-ol, mp 138.5–139.5 °C, was isolated with NMR δ ($CDCl_3$) 7.32 (5 H Ph pseudo s), 7.25 (4 H, C_6H_4 pseudo s), 3.02 (1 H t, J = 7 Hz, HCOH), 2.40 (3 H s, CH_3), 2.75–1.65 (6 H m, CH_2 and cyclopropyl H), 1.33 (1 H s, OH); ir (mull) 3350 (OH), 3050, 1600, 1500, 1480, 1360, 1320, 1120, 1080, 1040, 980, 860, 760, 700 cm^{-1}.

Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 85.55;[19] H, 7.67.

Hydroboration of 6-*endo*-*p*-methoxyphenyl-6-*exo*-phenylbicyclo[3.1.0]hex-2-ene, mp 90–91 °C, gave a good yield of the 2- and 3-ols; 6-*endo*-*p*-methoxyphenyl-6-*exo*-phenylbicyclo[3.1.0]hexan-3-ol, mp 151–152 °C, was isolated with NMR δ 6.8–7.4 (9 H Ar m with Ph at 7.10 covering the lower side of the A_2B_2 quartet), 3.82 (3 H s, CH_3), 2.95 (1 H t, J = 7 Hz, HCOH), 1.7–2.6 (6 H m CH_2 and cyclopropyl H), 1.33 (1 H s, OH); ir (mull) 3350 (OH), 3080, 3050, 1600, 1490, 1440, 1365, 1280, 1230, 1160, 1060, 1010, 830, 730, 690 cm^{-1}.

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 80.99; H, 7.32.

Europium Shift Reagent Studies. A sample of 20–25 mg of the 3-ol was dissolved in 0.5 ml of deuteriochloroform and the spectrum recorded at 1000-Hz sweep width. A weighed sample of commercially available $Eu(fod)_3$ (180–220 mg) was dissolved in a minimum volume of deuteriochloroform and the total solution was taken up in a 250-μl syringe so that the total volume of the solution could be measured. Then individual 5–20-μl aliquots were added to the tube and a spectrum was recorded. Additions were continued until the signal attributed to H_{at} was clearly delineated between the doublet due to H_{no} and the doublet due to H_{xo}. The induced shifts were plotted against the mole ratio (see Figure 1). The shifts were shown to correlate with $1/r^2$ where r is the distance from the oxygen lone pair lobes to the hydrogen atom as measured on Prentice–Hall models for the shallow chair conformation. Then distance and angle factors from the europium ion were included in the correlation. The europium ion center was positioned 3.0 Å from the alcohol oxygen so that the Eu–O axis was 130° from the C–O bond[14]. Then R, the distance from the europium ion to the hydrogen atom on the model, was measured with dividers, and θ, the angle between that vector and the Eu–O axis, was measured with a protractor. The results are given in Table I. The induced shifts at ca 1.4/1 mole ratio were extrapolated to 1/1 following the reported method.[13] Using his technique only 1/1 complexes are formed. Least-squares correlation coefficients were calculated on a standard program available with the cps package for an IBM 360-65.

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Registry No.—**1a**, 22524-13-6; **1b**, 57774-37-5; **1c**, 21884-57-1; **1d**, 21884-61-7; **1e**, 57774-38-6; **1f**, 57774-39-7; **3a**, 57774-40-0; **3b**, 57774-41-1; **3c**, 57774-42-2; **3d**, 57774-43-3; **3e**, 57774-44-4; **3f**, 57774-45-5.

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(19) This alcohol shows no trace of impurity by TLC, ir, or NMR, and it produces good needles on crystallization. However, three independent analyses even after drying overnight at 120 °C at 0.1 mm still gave low carbon analyses.

An Unexpected Decomposition of Triphenyl(methyl)stibonium Bromide under Mild Conditions

G. E. Parris,*[1] G. G. Long, B. C. Andrews, and R. M. Parris

North Carolina State University, Raleigh, North Carolina 27607

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In the course of a routine examination of the electrical conductance of a series of triphenyl(methyl)stibonium salts in acetonitrile at 25 °C, we observed that the electrical conductivity of triphenyl(methyl)stibonium bromide solutions decreased slowly with time (Table I).[2] In aged solutions, the ^1H NMR signals of triphenylstibine and methyl bromide as well as the signals of the triphenyl(methyl)stibonium cation were observed. The decomposition reaction[3]

$$(C_6H_5)_3SbCH_3^+Br^- \rightarrow (C_6H_5)_3Sb + CH_3Br$$

was studied conductimetrically. The kinetic results were initially baffling, but when ion-pairing and salt effects were accounted for, the data (Table II) were found to fit a second-order rate law of the form

$$\text{rate} = k^0\alpha^2C^2\frac{\gamma_A\gamma_B}{\gamma_{\neq}}$$

where k^0 is the rate constant, α is the degree of dissociation of the salt at total concentration C, and γ_A, γ_B, $\gamma_{\neq}$ are the activity coefficients of the ions (A, B) and transition state ($\neq$).

Table I. Decomposition of Triphenyl(methyl)stibonium Bromide in Acetonitrile at 25 °C

Run	Concn (C) $\times 10^3$ mol/l.	Initial conductance $\times 10^7$ ohm^{-1}	mol/l. / ohm^{-1}	Rate $\times 10^9$ ohm^{-1}/s	Rate $\times 10^9$ mol/l. s
3	5.987	36 249	1.6516	1.616	2.670
1	5.234	33 897	1.5450	1.475	2.278
1	3.604	22 446	1.4062	0.8483	1.193
3	3.085	22 459	1.3742	0.8225	1.130
2	2.849	21 255	1.3404	0.7848	1.052
1	1.802	14 750	1.2230	0.3883	0.4749
3	1.462	12 157	1.2025	0.2863	0.3443
2	1.425	12 000	1.1875	0.2458	0.2919
3	0.7803	7 041	1.1082	0.1107	0.1226
1	0.7208	6 758	1.0670	0.1233	0.1316

Table II. Behavior of Triphenyl(methyl)stibonium Bromide in Acetonitrile at 25 °C[a]

Run	Concn (C) × 10^3 mol/l.	Λ	Λ_x	α	k = rate/α^2C^2 × 10^5 l mol^{-1} s^{-1}	$\sqrt{\alpha C}$ × 10^2
3	5.987	80.0	126.4	0.633	18.60	6.16
1	5.234	85.4	127.0	0.672	18.40	5.93
1	3.604	93.4	129.3	0.723	17.58	5.10
3	3.085	96.0	130.1	0.737	21.82	4.77
2	2.849	98.3	130.5	0.752	22.98	4.63
1	1.802	107.0	132.7	0.806	22.52	3.81
3	1.462	109.8	133.7	0.821	23.90	3.46
2	1.425	110.7	133.7	0.828	20.98	3.43
3	0.7803	118.6	136.0	0.872	26.48	2.61
1	0.7208	121.1	136.2	0.889	32.03	2.53

[a] Λ = observed molar conductance; Λ_x = molar conductance expected in the absence of ion pairing; Λ_x was determined by an iterative process using the Kohlrausch–Onsager equation $\Lambda_x = \Lambda_0 - S[\Lambda/\Lambda_x C]^{1/2}$, $S = 0.7374\Lambda_0 + 233.6$, Λ_0 for $(C_6H_5)_3SbCH_3Br$ = 143; α = degree of dissociation = $\Lambda/\Lambda_x = [Br^-]/C = [(C_6H_5)_3SbCH_3^+]/C$; C = total salt concentration; $\alpha C = \mu$ = ionic strength.

In agreement with the Debye–Hückel theory,[4] we found that a plot of log (rate/α^2C^2) vs. the square root of ionic strength gives a straight line plot for the data from which $k^0 = 3.4 \times 10^{-4}$ M^{-1} s^{-1} was determined by extrapolation of the data for run 3. The theoretical slope based on the dielectric constant of acetonitrile (35.95)[5] is −3.28; the experimental slope was −4.32.

$$\log \frac{\text{rate}}{\alpha^2C^2} = \log k^0 + \log (\gamma_A\gamma_B/\gamma_{\neq})$$

$$\log \gamma_A\gamma_B = 2Z_AZ_BA\sqrt{\mu}$$

where $\gamma_{\neq} = 1$, $A = 1.64$ for dielectric constant 35.95, Z_A and Z_B are the ionic charges (+1, −1), and μ is the ionic strength which in this case is equal to αC at any concentration.

In theory k^0 is the sum of two contributions in the form $k^0 = k_1^0k_A + k_2^0$, where k_1^0 is the rate constant for collapse of ion pairs, k_A is the ion association constant, and k_2^0 is the rate constant for direct reaction of free ions. However, it is impossible to separate k^0 into its parts for the reasons discussed by Pocker and Parker.[3]

As calculated from electrical conductance measurements, the degree of dissociation of the salt varied from 0.633 at 5.99×10^{-3} M to 0.889 at 0.721×10^{-3} M. During the course of the study, the limiting ionic conductances of triphenyl(methyl)stibonium cation (47 ± 5), tetraphenylstibonium cation (41 ± 4), and BF_4^- anion (104 ± 7) were estimated. The values are reasonable compared to the ionic conductances of tetraphenylarsonium cation (55.8) and perchlorate anion (103.8) reported in the literature.[6,7]

Experimental Section

Triphenyl(methyl)stibonium tetrafluoroborate was prepared by treating triphenylstibine with trimethyloxonium tetrafluoroborate in boiling methylene chloride for 2.5 h. Anal. Calcd for $C_{19}H_{18}SbBF_4$: C, 50.17; H, 4.00; Sb, 26.76. Found: C, 50.45; H, 4.06; Sb, 26.51. The bromide salt was prepared by adding the corresponding potassium salt to a solution of the stibonium tetrafluoroborate in 95% ethanol and removal of the precipitated KBF_4 by filtration. Anal. Calcd for $C_{19}H_{18}SbBr$: C, 50.94; H, 4.05; Sb, 27.18. Found: C, 50.67; H, 4.11; Sb, 27.32. Carbon and hydrogen analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and antimony analyses were performed by Mrs. D. E. Knight at N.C.S.U.

Acetonitrile was purified for conductance measurements by standing over NaOH pellets and molecular sieve for several days followed by distillation through a column packed with molecular sieve. The specific conductance of the solvent used in the measurements was usually 30×10^{-7} ohm^{-1} cm^{-1} at 25 °C, but no significant difference was noted using solvent with specific conductance as high as 200×10^{-7} ohm^{-1} cm^{-1} provided this correction was applied to the measured conductances of salt solutions.

Conductance and kinetic measurements were made in an enclosed fill-type Beckman cell with cell constant 0.1320 ± 0.0003 cm^{-1}. The cell was kept in a bath which was maintained at 25.0 ± 0.2 °C. A Beckman RC-18A bridge was used to measure conductance.

The kinetic runs were made by two different techniques. Preliminary runs (1 and 2) were made by making up a large volume of stock solution from which dilutions were made. The diluted solutions were stored in a thermostated Dewar flask and their conductances were measured periodically by transferring samples into the conductance cell. All manipulations were made in the air. Later runs (run 3) were made by accurately weighing samples of the salt into 25-ml volumetrics and transferring the volumetrics into a nitrogen-flushed glove box. Acetonitrile was added and the salt rapidly dissolved. The cell was rinsed with three small portions (~3 ml each) of the solution and the remaining solution was just sufficient to fill the cell. The cell was closed with its ground glass thermometer, taken out of the glove box, and placed in the thermostated bath. The first conductance measurements were made approximately 15 min after adding solvent and the sample was monitored continuously for up to 1500 min without disruption. While the preliminary runs showed some scatter in the results, the latter technique produced a very consistent set of data.

Registry No.—Triphenyl(methyl)stibonium bromide, 58074-28-5; triphenyl(methyl)stibonium tetrafluoroborate, 3802-09-3; triphenylstibine, 603-36-1; trimethyloxonium tetrafluoroborate, 420-37-1.

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Photocyclization of 3-(3-Methyl-2-butenyloxy)- and 3-(3-Methyl-2-butenylamino)-5,5-dimethyl-2-cyclohexen-1-ones to 7-Oxa- and 7-Azabicyclo[4.3.0]nonan-2-ones

Yasumitsu Tamura,* Hiroyuki Ishibashi, and Masazumi Ikeda

Faculty of Pharmaceutical Sciences, Osaka University, 133-1, Yamada-kami, Suita, Osaka, Japan

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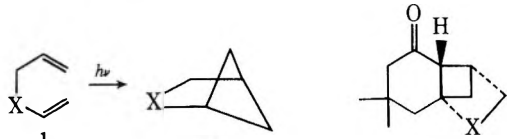
In a preceding paper,[1] we have shown that the photocycloaddition reaction of 1,5-hexadienes to bicyclo[2.1.1]hexanes[2] [1 (X = CH_2) → 2] can be extended to the syntheses of 2-oxa- and 2-azabicyclo[2.1.1]hexane ring systems [1 (X

= O or NR) → 2]; e.g., compounds **3** were synthesized from 3-allyloxy- and 3-allylmethylamino-5,5-dimethyl-2-cyclohexen-1-ones. In continuation of our studies directed

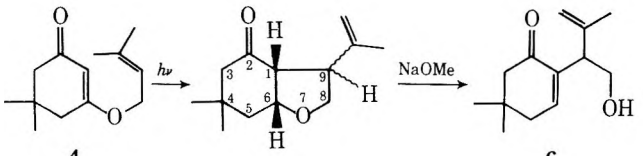


1 2 3, X = O or NMe

toward the utilization of this reaction in the syntheses of the heterocyclic compounds, we have examined the photochemical behavior of 3-(3-methyl-2-butenyloxy)- and 3-(*N*,3-dimethyl-2-butenylamino)-5,5-dimethyl-2-cyclohexen-1-ones (**4** and **10**), and found the exclusive formation of 7-oxa- and 7-azabicyclo[4.3.0]nonan-2-one ring systems (**5** and **11**).

Compound **4** was prepared by the procedure used to synthesize 3-(3-methyl-2-butenyloxy)-2-cyclohexen-1-one:[3] treatment of the silver salt of dimedone with 1-bromo-3-methyl-2-butene in refluxing anhydrous benzene gave 18% yield of **4**.

Irradiation of a 0.7% cyclohexane solution of **4** with a 350-W high-pressure mercury lamp in a Pyrex tube for 15 h resulted in the formation of an oily isomeric ketone **5** in 69% yield. The assignment of structure **5** is based on its



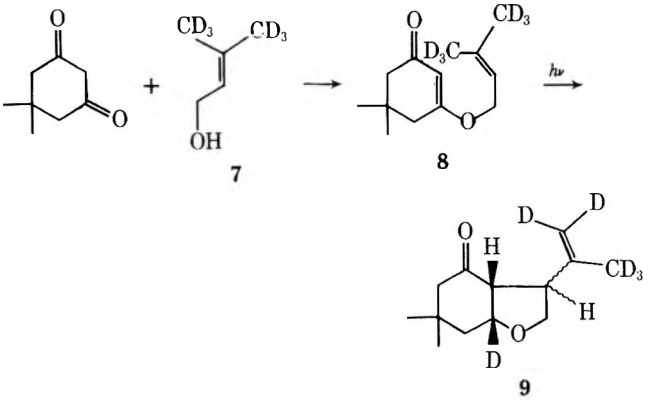
4 5 6

composition, spectra, and subsequent transformation. Compound **5** shows ir bands at 3080, 1710 (six-membered ketone), 1645, and 900 cm^{-1} (C=CH_2) and a well-resolved NMR spectrum (see Experimental Section). The assignments were confirmed by spin decoupling experiments and deuterium labeling experiments (vide infra). Irradiation of 6-H at τ 5.56 caused the doublet of doublets of 1-H at τ 7.28 to collapse to a doublet, J = 6.0 Hz, and the doublet of 5-H at τ 8.17 to a singlet, and irradiation of 1-H at τ 7.28 converted the doublet of triplets of 6-H into a broad triplet, J = 5.6 Hz, and the doublet of triplets of 9-H at τ 6.64 into a broad triplet, J = 8.0 Hz. Irradiation of 9-H converted triplets of 8-H at τ 5.94 and 6.42 to doublets, J = 8.0 Hz, the signal of 1-H to a doublet, J = 7.0 Hz, and the broad signal of olefinic protons to a sharp signal. The ketone **5** was cleaved by sodium methoxide in methanol to enone **6**, whose structure was assigned on the basis of its composition and spectral evidence (see Experimental Section).

The stereochemistry of 1-H and 6-H was tentatively assigned on the basis of the spin-coupling pattern (7.0 Hz). This value appears to be reasonable if these protons were cis to each other. In this orientation the dihedral angle between the two protons is 25–30°. If the protons were trans oriented the resulting dihedral angle (~170°) would require larger spin interaction.

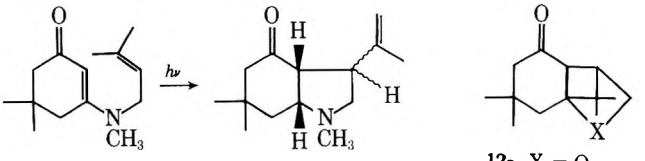
The formation of **5**[4] may be considered as a photochemical intramolecular "ene" reaction,[5] and only two examples of this type of reaction are known: transformations of citral[6,7] and 6-methyl-1,5-heptadien-3-one[8] into 2-isopropenyl-5-methylcyclopentan-1-aldehyde (18% yield) and 3-isopropenylcyclopentanone (10% yield), respectively.

The intramolecularity of this reaction was unequivocally proved by the following deuterium labeling experiments. Deuterated compound **8** was prepared by treating dimedone with dimethylallyl-*3,3-d*$_6$ alcohol (**7**) which was in turn synthesized by the reaction of acetone-d_6 and ethoxycarbonylmethylenetriphenylphosphorane followed by lithium aluminum hydride reduction of the resulting ethyl dimethylacrylate-*3,3-d*$_6$. Irradiation of **8**, carried out as described for **5**, afforded **9**, whose NMR spectrum (see Experimental Section) clearly indicated the absence of the signals due to 6-H and the isopropenyl group.



7 8 9

Under the similar conditions described for **5**, irradiation of **10**, prepared by treating dimedone with *N*,3-dimethyl-2-butenylamine, gave a 66% yield of an oily amine **11** as a sole product, which was characterized as the picrate, mp 142–143 °C. The gross structure of **11** was assigned on the



10 11 12a, X = O; 12b, X = NCH_3

basis of the spectral comparison with **5**. Thus, its ir spectrum displays 3080, 1705 (six-membered ketone), 1640, and 895 cm^{-1} (C=CH_2) and its NMR spectrum (see Experimental Section) is well resolved; the coupling constant between 1-H and 6-H is 7.5 Hz, and that between 1-H and 9-H is 5.0 Hz, which are consistent with those of **5**, suggesting that **11** has a stereochemical arrangement identical with that of **5**.

Finally, it should be noted that 2-oxa- and 2-azabicyclo[2.1.1]hexane derivatives **12a** and **12b** were not detected by the NMR spectra and GLC analyses of the crude products after the photoirradiation of **4** and **10**.

Experimental Section

Melting points and boiling points are uncorrected. NMR spectra were determined with a Varian HA-100 (for **5** and **11**), and a Hitachi R-20A spectrometer (for the other compounds). Ir spectra were recorded with a Hitachi EPI-G2 spectrophotometer and uv spectra with a Hitachi 124 spectrophotometer. Mass spectra were obtained with a Hitachi RMU-6D with a direct inlet system operating at 70 eV. Preparative TLC was carried out on Merck alumina PF_{254}. Photoirradiation was carried out in a Pyrex tube using an Eikosha 350-W high-pressure mercury lamp.

3-(3-Methyl-2-butenyloxy)-5,5-dimethyl-2-cyclohexen-1-one (4). A suspension of the silver salt of dimedone (prepared from 7.7 g of $AgNO_3$ and 2.7 g of dimedone by application of the method of Woods and Tucker[9]) and 4.47 g of 1-bromo-3-methyl-2-butene in 40 ml of anhydrous benzene was refluxed for 20 min with vigorous stirring. The insoluble material was filtered off and the filtrate was washed with 10% sodium hydroxide and a saturated NaCl solution and dried ($MgSO_4$). The solvent was removed and the residual liquid distilled to give 1.1 g (18%) of **4** as a colorless oil: bp 100–102 °C (0.12 mm); ir ($CHCl_3$) 1640, 1605 cm^{-1}; uv max (EtOH) 251 nm (log ϵ 4.19); NMR ($CDCl_3$) τ 4.45–4.80 [m, 1, -CH=C(CH_3)$_2$], 4.64 (s, 1, 2-H), 5.65 (bd, 2, J = 7 Hz, OCH_2), 7.77

(s, 2, 6-H), 7.84 (s, 2, 4-H), 8.25 and 8.33 (s × 2, 3 × 2, CH=C(CH_3)$_2$], 8.95 [s, 6, $CH_2C(CH_3)_2$]; mass spectrum *m/e* 208 (M^+).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.64; H, 9.47.

4,4-Dimethyl-9-isopropenyl-7-oxabicyclo[4.3.0]nonan-2-one (5). A solution of 265 mg of 4 in 40 ml of cyclohexane was irradiated for 15 h. The solvent was removed and the residual liquid was submitted to preparative TLC using petroleum ether (bp 30–60 °C)–ether (3:2) as solvent to give 182 mg (69%) of **5** as a colorless oil: bp 85–90 °C (bath temperature) (0.03 mm); ir ($CHCl_3$) 3080, 1710, 1645, 1060, 900 cm^{-1}; NMR ($CDCl_3$, 100 MHz) τ 5.16 (s, 2, C=CH_2), 5.56 (dt, 1, *J* = 7.0 and 5.6 Hz, 6-H), 5.94 (t, 1, *J* = 8.0 Hz, 8-H), 6.42 (t, 1, *J* = 8.0 Hz, 8-H), 6.64 (td, 1, *J* = 8.0 and 6.0 Hz, 9-H), 7.28 (dd, 1, *J* = 7.0 and 6.0 Hz, 1-H), 7.77 (center of AB q, 2, *J* = 14.0 Hz, 3-H), 8.17 (d, 2, *J* = 5.6 Hz, 5-H), 8.26 [t, 3, *J* = 2.0 Hz, C(CH_3)=CH_2], 8.97 and 8.99 [s × 2, 3 × 2, C(CH_3)$_2$]; mass spectrum *m/e* 208 (M^+).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.66; H, 9.47.

2-(1-Hydroxymethyl-2-methyl-2-propenyl)-5,5-dimethyl-2-cyclohexen-1-one (6). A solution of 100 mg of **5** and 10 mg of sodium methoxide in 2 ml of methanol was refluxed for 1 h. After the solvent was removed, anhydrous ether was added. The insoluble material was filtered off, and the filtrate was dried ($MgSO_4$) and concentrated. The residual liquid was submitted to preparative TLC using petroleum ether (bp 30–60 °C) as solvent to give 64 mg (64%) of **6** as a colorless oil: ir ($CHCl_3$) 3450, 1660, 900 cm^{-1}; uv max (EtOH) 235 nm (log ϵ 3.91) (calcd for 2-alkyl-2-cyclohexen-1-one, 237 nm); NMR ($CDCl_3$) τ 3.30 (t, 1, *J* = 5 Hz, 3-H), 5.05 and 5.22 (bs × 2, 2, C=CH_2), 6.20–6.50 (m, 3, $CHCH_2OH$), 7.73 (s, 2, 6-H), 7.79 (s, 1, OH), 8.15–8.40 [m, 5, 4-H and CH_2=C(CH_3)], 9.00 [s, 6, C(CH_3)$_2$]; mass spectrum *m/e* 208 (M^+).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.66; H, 9.47.

Ethyl Dimethylacrylate-*3,3-d*$_6$. The procedure of Fodor and Tömösközi[10] was employed. A mixture of 1.92 g of acetone-d_6 and 10.44 g of ethoxycarbonylmethylenetriphenylphosphorane was heated in a sealed tube at 120 °C for 24 h. To the reaction mixture was added anhydrous petroleum ether and insoluble triphenylphosphine oxide was filtered off. The filtrate was concentrated and distilled to give 860 mg (21%) of ethyl dimethylacrylate-*3,3-d*$_6$: bp 62–63 °C (30 mm); ir ($CHCl_3$) 2200, 1705, 1640, 1165 cm^{-1}; NMR ($CDCl_3$) τ 4.36 [s, 1, CH=C(CD_3)$_2$], 5.88 (q, 2, CH_2CH_3), 8.77 (t, 3, CH_2CH_3); mass spectrum *m/e* 134 (M^+).

Dimethylallyl-*3,3-d*$_6$ Alcohol. A solution of 700 mg of ethyl dimethylacrylate-*3,3-d*$_6$ in 3 ml of anhydrous ether was slowly added to a suspension of 200 mg of lithium aluminum hydride in 5 ml of anhydrous ether. The reaction mixture was refluxed for 12 h. After an usual work-up procedure, dimethylallyl-*3,3-d*$_6$ alcohol was obtained in 48% yield (250 mg): bp 55–60 °C (15 mm); ir ($CHCl_3$) 3580, 2200, 1660 cm^{-1}; NMR ($CDCl_3$) τ 4.60 [t, 1, *J* = 7.0 Hz, CH=C(CD_3)$_2$], 5.90 (d, 2, *J* = 7.0 Hz, CH_2OH), 8.00 (s, 1, OH); mass spectrum *m/e* 92 (M^+).

3-(Dimethylallyloxy-*3,3-d*$_6$)-5,5-dimethyl-2-cyclohexen-1-one (8). A solution of 80 mg of dimedone and 160 mg of dimethylallyl-*3,3-d*$_6$ alcohol in 5 ml of benzene containing of 3 mg of *p*-toluenesulfonic acid was refluxed for 7 h using a Dean-Stark water separator. After removal of the solvent, the residual liquid was submitted to preparative TLC using petroleum ether (bp 30–60 °C)–ether (1:1) as solvent to give 70 mg (57%) of **8** as a colorless oil: ir ($CHCl_3$) 2230, 2180, 1640, 1605 cm^{-1}; NMR ($CDCl_3$) τ 4.58 [t, 1, *J* = 7.0 Hz, CH=C(CD_3)$_2$], 4.64 (s, 1, 2-H), 5.65 (d, 2, *J* = 7.0 Hz, OCH_2), 7.77 (s, 2, 6-H), 7.84 (s, 2, 4-H), 8.95 [s, 6, C(CH_3)$_2$]; mass spectrum *m/e* 214 (M^+).

Irradiation of 8. A solution of 60 mg of **8** in 10 ml of cyclohexane was irradiated for 12 h. The solvent was removed and the residual liquid was submitted to preparative TLC using petroleum ether (bp 30–60 °C)–ether (3:2) as solvent to give 37 mg (62%) of **9** as a colorless oil: ir ($CHCl_3$) 2180, 2120, 1710, 1605 cm^{-1}; NMR ($CDCl_3$) τ 6.00 (t, 1, *J* = 8.0 Hz, 8-H), 6.44 (t, 1, *J* = 8.0 Hz, 8-H), 6.70 (ddd, 1, *J* = 8.0, 8.0, and 6.0 Hz, 9-H), 7.35 (d, 1, *J* = 6.0 Hz, 1-H), 7.81 (s, 2, 3-H), 8.23 (s, 2, 5-H), 9.04 [s, 6, C(CH_3)$_2$]; mass spectrum *m/e* 214 (M^+).

3-(*N*,3-Dimethyl-2-butenylamino)-5,5-dimethyl-2-cyclohexen-1-one (10). A solution of 140 mg of dimedone and 220 mg of *N*,3-dimethyl-2-butenylamine in 5 ml of benzene was heated in a sealed tube at 100 °C for 7 h. The solvent was removed and the residual liquid distilled to give 206 mg (93%) of **10** as a yellow oil: bp 160–170 °C (bath temperature) (0.08 mm); ir ($CHCl_3$) 1605, 1550 cm^{-1}; NMR ($CDCl_3$) τ 4.47–5.38 [m, 1, CH=C(CH_3)$_2$], 4.88 (s, 1, 2-H), 6.18 (bd, 2, *J* = 7.0 Hz, CH_2CH=), 7.18 (s, 3, NCH_3), 7.79 (s, 2, 6-H), 7.91 (s, 2, 4-H), 8.30 and 8.36 [bs × 2, 3 × 2, CH=C(CH_3)$_2$], 8.97 [s, 6, C(CH_3)$_2$]; mass spectrum *m/e* 221 (M^+).

Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.71; H, 10.55; N, 6.10.

4,4,7-Trimethyl-9-isopropenyl-7-azabicyclo[4.3.0]nonan-2-one (11). A solution of 102 mg of **10** in 25 ml of cyclohexane was irradiated for 5 h. The solvent was removed and the residual liquid was submitted to preparative TLC using petroleum ether (bp 30–60 °C)–ether (3:2) as solvent to give 67 mg (66%) of **11** as a colorless oil: ir ($CHCl_3$) 3080, 1705, 1640, 895 cm^{-1}; NMR (CCl_4, 100 MHz) τ 5.30 (bs, 2, C=CH_2), 6.60–6.85 (m, 1, 9-H), 6.93 (t, 1, *J* = 8.0 Hz, 8-H), 7.32 (td, 1, *J* = 7.5 and 4.8 Hz, 6-H), 7.53 (dd, 1, *J* = 7.5 and 5.0 Hz, 1-H), 7.82 (s, 3, NCH_3), 7.87 (s, 2, 3-H), 8.00 (t, 1, *J* = 8.0 Hz, 8-H), 8.30 [bs, 3, C(CH_3)=CH_2], 8.33 (d, 2, *J* = 4.8 Hz, 5-H), 8.96 and 8.98 [s × 2, 3 × 2, C(CH_3)$_2$]. Spin decoupling experiments show the following results. Irradiation of 6-H at τ 7.32 caused the doublet of 5-H at τ 8.33 to collapse to a singlet, and irradiation of the multiplet of 9-H converted the doublet of doublets of 1-H at τ 7.53 to the doublet, *J* = 7.5 Hz, and triplets of 8-H at τ 6.93 and 8.00 to doublets, *J* = 8.0 Hz. Irradiation of 1-H converted the signal of 9-H to a broad triplet, *J* = 8.0 Hz; mass spectrum *m/e* 221 (M^+).

It formed a picrate, mp 142–143 °C (from EtOH).

Anal. Calcd for $C_{20}H_{26}N_4O_8$: C, 53.33; H, 5.82; N, 12.44. Found: C, 53.76; H, 6.06; N, 12.53.

Registry No.—**4**, 57969-26-3; **5**, 57969-27-4; **6**, 57969-28-5; **7**, 53439-16-0; **8**, 57969-29-6; **9**, 57969-30-9; **10**, 57969-31-0; **11**, 57969-32-1; **11** picrate, 57969-33-2; dimedone, 126-81-8; 1-bromo-3-methyl-2-butene, 870-63-3; ethyl dimethylacrylate-*3,3-d*$_6$, 53439-15-9; *N*,3-dimethyl-2-butenylamine, 29151-30-2.

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(4) Energy transfer experiments using piperylene showed that the reaction **4** → **5** was not quenched even by high concentration. For example, when a solution of 0.1 M of piperylene and 0.01 M of **4** in ether was irradiated, product **5** was obtained at a similar rate to that of the reaction without piperylene. The result is in contrast to the case of the formation of **3** (X = NMe),[1] and suggests that this reaction involves a singlet excited state of the enone **4**.
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Photochemical Studies on Alkyl Amides

Paul H. Mazzocchi* and Michael Bowen[1]

Department of Chemistry, University of Maryland, College Park, Maryland 20742

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Although there are numerous studies reported on the photochemistry of aldehydes and ketones,[2] there have been only a few reports on the photochemistry of esters[3] and amides.[4–6] In the case of amides in particular the two major reports are contradictory.

Booth and Norrish[4] studied the photochemistry of a series of alkyl amides by examination of the gaseous products from the reaction in dioxane and hexane. They observed alkenes from the C_4, C_5, and C_6 amides and inferred that they were ethylene, propene, and butene. On the basis of these results they suggested that the type II process (eq 1) was the major one occurring. Chemical tests indicated that primary amines but no aldehydes or diketones were present, and, although CO was isolated in all instances, no

methane was obtained from acetamide. These workers suggested that α-cleavage processes (eq 2 and 3) were not important.

$$RCH_2CH_2CH_2CONH_2 \xrightarrow{h\nu} RCH{=}CH_2 + CH_3CONH_2 \quad (1)$$

$$RCONH_2 \xrightarrow{h\nu} \cdot CONH_2 + R\cdot \xrightarrow[\text{solvent}]{\sim H} RH \quad (2)$$

$$RCONH_2 \xrightarrow{h\nu} \cdot NH_2 + RCO\cdot \xrightarrow[\text{solvent}]{\sim H} RCHO \quad (3)$$

$$RCONH_2 \xrightarrow{h\nu} RNH_2 + CO \quad (4)$$

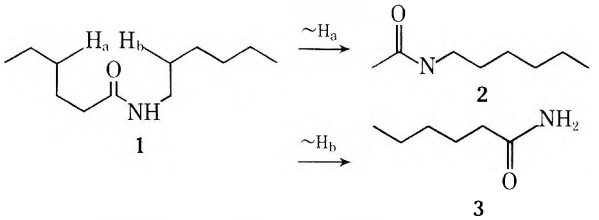
Nicholls and Leermakers[5] subsequently reexamined the photochemistry of a number of amides at 254 nm and noted that prolonged irradiation of primary and secondary amides resulted in no disappearance of starting material but that tertiary amides did decompose under those conditions (Φ = 0.10–0.16). Although the reaction mixture was complex, GLC analysis showed that no type II products (e.g., *N,N*-dimethylacetamide from *N,N*-dimethylbutyramide) were formed. They suggested that the α-cleavage (type I) reaction (eq 3) was occurring.

Our interest in the photochemistry of amides[6b,c] and lactams led us to reexamine this problem to see if isolation and characterization of some of the solvent derived products formed might provide a clue to resolve these apparently contradictory results.

Results

Irradiation of primary and secondary amides with λ >250 nm indicated that no photodegradation was occurring, but starting material did disappear when irradiation was carried out through Vycor or with an unfiltered (quartz) source.

Preliminary investigations were conducted in a number of solvents on *N*-hexylhexanamide (**1**). Irradiations were conducted in methanol, acetonitrile, diisopropyl ether, dioxane, and cyclohexane and, although GLC traces were complex, especially in the latter two solvents, peaks corresponding to type II products **2** and **3** were detected in all cases, but in no case was the sum of the yields of **2** + **3** >3% based on starting material disappearance.

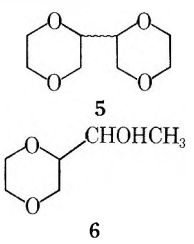


We demonstrated that the products (**2** and **3**) were not undergoing an (unexpected) preferential reaction by irradiating known mixtures of **1**, 2, and **3**.

Product Isolation. Dioxane Solvent. A number of amides (**4a–f**) were irradiated in dioxane solution and the reaction mixtures analyzed by GLC. In all cases the formation of four products was noted. These products were isolated (preparative GLC) from a photolysis of **1** and characterized as a pair of diastereomeric dioxane dimers[7] (**5**) and the diastereomeric solvent derived alcohols (**6**).[8] The formation of **5** is a clear indication that free-radical processes are occurring whereas the formationf **6** suggests that acetaldehyde is formed and subsequently undergoes photoreduction in dioxane.[8,9] Butene and *n*-pentane were also detected in the reaction mixture from **1** and infrared analysis of the head space gases indicated the presence of carbon monoxide.

RCONHR′

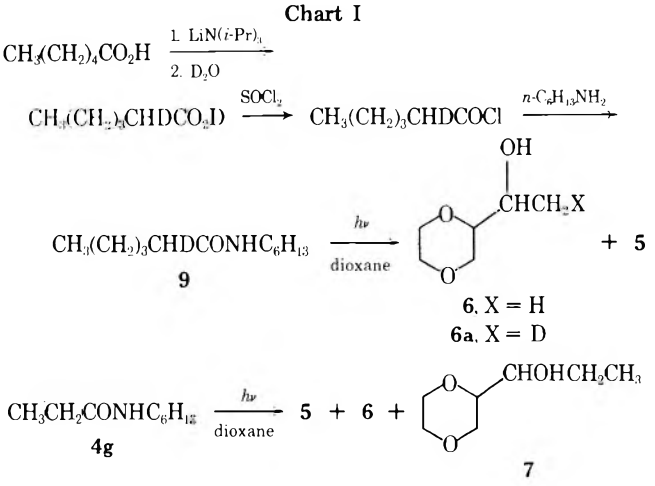
4a, R = CH_3; R′ = C_6H_{13}
b, R = C_7H_{15}; R′ = C_6H_{13}
c, R = C_5H_{11}; R′ = H
d, R = C_5H_{11}; R′ = CH_3
e, R = C_7H_{15}; R′ = H
f, R = C_2H_5; R′ = H
g, R = C_2H_5; R′ = C_6H_{13}



Since we had demonstrated that **6** is a product of the direct irradiation of dioxane,[8] although it appears to be generated with much greater efficiency in the present instance, it was necessary to show that **6** was at least partially amide derived. Two experiments were performed addressing this question.

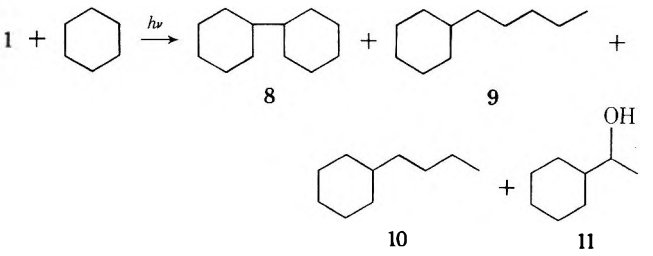
α-Deuterio-*N*-hexylhexanamide (**9**, 28% α-d_1) was prepared from the labeled acid[10] (Chart I), irradiated in dioxane solution, and the alcohols **6** and **6a** were isolated by preparative GLC. Mass spectral analysis showed a **6**/**6a** ratio of 23, indicating that approximately 85% of the product was solvent derived and only 15% was the direct result of amide photolysis.

Chart I



In a second experiment, irradiation of **4g** in dioxane afforded, in addition to **5** and **6**, alcohols **7**. Clearly **7** is an amide-derived product since it is not produced from dioxane alone but presumably arises via the intermediate formation of propionaldehyde.

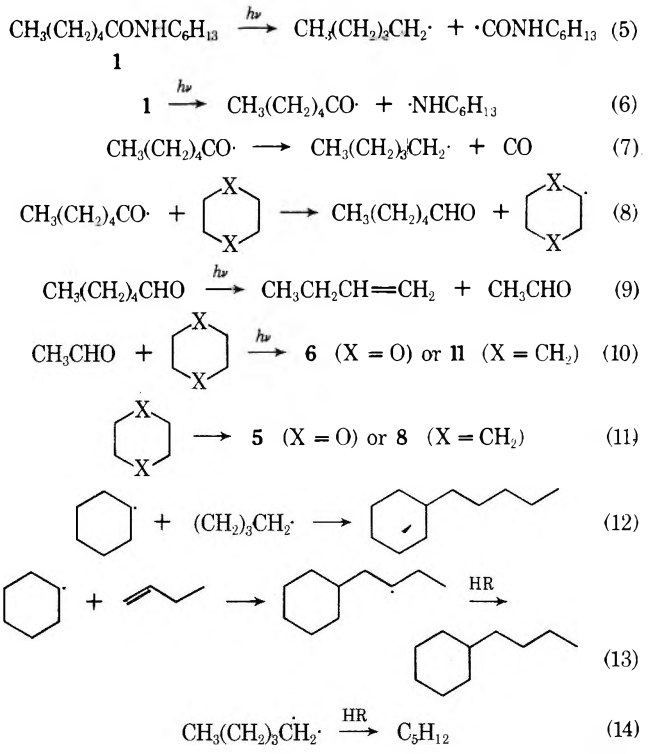
Cyclohexane Solvent. In view of the reactivity of dioxane under the photolysis conditions, a study was conducted in cyclohexane. The GLC trace of the 1-cyclohexane photolysate was exceedingly complex, consisting of one major and numerous minor peaks.[11] Four of these were isolated in pure form and identified as butylcyclohexane (**10**), pentylcyclohexane (**9**), bicyclohexyl (**8**), and α-methylcyclohexanemethanol (**11**). *n*-Pentane was detected (GLC) but hexylcyclohexane was shown to be absent. A sample of **1** was irradiated in the presence of an internal standard and the yields of **8** (33%), **9** (5%), **10** (2%), and **11** (1%) determined.[12]



The complexity of the amide photolysis has already been noted. Although no primary products were isolated and it is difficult to relate the yields of secondary products to the

efficiencies of the primary photochemical acts,[12] several conclusions can be reached. We suggest the sequence outlined in Scheme I to explain the observed products. The

Scheme I



formation of radical initiated products **5** and **6** and the appearance of **2** and **3** as only minor products indicates that type I cleavages (eq 5 and/or 6) are the major processes occurring.

The absence of the expected aldehydes in the reaction mixture can be rationalized by the sequence eq 8–10. Under the reaction conditions hexanal, which has its n → π^* absorption at 290 nm, is immediately exposed to light, and undergoes a type II reaction affording acetaldehyde and the previously observed 1-butene. Acetaldehyde then undergoes photoreduction to the alcohol **6**, in which form it is immune to chemical tests for aldehydes whereas at least a portion of the 1-butene appears as **10** in the cyclohexane experiments. These experimental results and the formation of **8**, **9**, and **11** in cyclohexane (eq 10–14) are consistent with those of Booth and Norrish.[4] We observe no aldehyde products since the aldehydes formed undergo secondary photoreduction to give alcohols. We also observe alkenes but our evidence suggests that they arise largely from secondary photochemical reactions of intermediate products (aldehydes) and not directly from type II reactions of amides.

Our conclusions essentially agree with those of Nicholls and Leermakers, i.e., we find that the type II process in amides is quite inefficient with respect to the type I cleavage.

Experimental Section

Infrared (ir) spectra were taken on a Perkin-Elmer 337 or a Beckman IR-8 grating spectrometer. NMR spectra were obtained in $CDCl_3$ solution (unless otherwise noted) on a Varian A-60D spectrometer at ambient temperature. Ultraviolet (uv) spectra were obtained on a Cary 15 spectrophotometer in cyclohexane. Mass spectra were obtained on a Du Pont 492 double focusing spectrometer. GLC work was carried out on a Varian Aerograph Model 1200 gas chromatograph or on a Varian Aerograph Model 90-P. Columns employed in GLC work follow: column A, 6 ft × 0.25 in., 15% DC550 on 80/100 Chromosorb W; column B, 6 ft × 0.125 in., 20% Versamid on 60/80 Chromosorb W; column C, 6 ft × 0.125 in., 15% DC550 on 80/100 Chromosorb W; column D, 6 ft × 0.125 in., 20% XE60 on Chromosorb W. Matheson Coleman and Bell spectrograde dioxane and cyclohexane from freshly opened bottles were used without further purification. Authentic bicyclohexyl, butylcyclohexane, pentylcyclohexane, and hexylcyclohexane were obtained from Chemical Samples Co. Mass spectra were taken by Dr. M. Gay and microanalyses were performed by Dr. Franz Kasler of the University of Maryland.

Photolysis Procedure. Two percent solutions of the amide in an appropriate solvent were purged with nitrogen for a minimum of 30 min and sealed with rubber serum caps. Samples were irradiated with a Hanovia 450-W Type L lamp through quartz for periods of 4–140 h and progress of the reaction was monitored by GLC. In preparative runs solvent was removed by distillation and product mixtures separated from the usual extensive polymeric residue by vacuum distillation. Separation of products was accomplished by preparative GLC.

***N*-Hexylhexanamide (1) in Dioxane.** A solution of 4 g of **1** in 200 ml of spectrograde dioxane was irradiated for 135 h. The solution was cooled in an ice bath. An infrared spectrum of the gas over the solution showed the presence of carbon monoxide. GLC analysis on columns C (35 °C), B (60 °C), and D (60 °C) indicated the presence of *n*-pentane and 1-butene. Work-up by GLC on column A (110 °C) gave the alcohols **6** and the dimers **5** identified by spectral comparison with authentic samples. Irradiation and GLC analysis of samples of **4a–f** indicated that starting material was disappearing and **5** and **6** were produced in all cases.

***N*-Hexylpropionamide in Dioxane.** Irradiation was carried out via the general procedure. GLC work-up gave, in addition to **5** and **6**, the diastereomeric alcohols **7a** and **7b**.[14] The ratio **6**/**7** was estimated to be ≃4.

7a: NMR δ 1.0 (t, 3), 1.15–1.75 (m, 2), 3.1–4.1 (m, 9); ir (CCl_4) 3600, 3550–3300, 2965, 2910, 2875, 2860, 1450, 1115 cm^{-1}, MS *m/e* 146 (P, 0.2), 128 (0.40), 117 (3.6), 87 (44), 59 (62), 58 (51), 57 (76), 45 (83), 44 (69), 43 (66), 31 (100).

7b: NMR δ 0.98 (t, 3), 1.2–1.8 (m, 2), 3.2–4.1 (m, 9); ir (CCl_4) 3650–3300, 2975, 2930, 2875, 1450, 1115 cm^{-1}; MS *m/e* 146 (P, 1.5), 128 (0.6), 117 (7.1), 87 (62), 59 (100), 58 (24), 57 (56), 45 (88), 44 (82), 43 (56), 37 (91).

Irradiation of propionamide in dioxane also gave **5**, **6**, and **7**.

***N*-Hexylhexanamide (1) in Cyclohexane.** A solution of 4 g of **1** in 210 ml of cyclohexane was irradiated for 115 h. Work-up by preparative GLC on column A gave **8**, **9**, **10**, and **11**,[14] identified by comparison of NMR, ir, and mass spectra with those of authentic samples. Yields were determined in a separate experiment in which 0.6646 g of **1** (with hexadecane internal standard) was irradiated and sampled after 4 (20% conversion), 8, and 13 h. Yields were calculated assuming a molar correspondence of 1 reacted and product formed.

Hexanal in Dioxane. A solution of 2.5 g of hexanal in 250 ml of dioxane was irradiated for 1.5 h. GLC analysis (column C, 40 °C) at 30-min intervals showed the rapid disappearance of hexanal and buildup of acetaldehyde, 1-butene, and *n*-pentane. The hexanal had almost completely disappeared after 1.5 h.

Preparation of *N*-Hexylhexanamide-α-d_1 (9). A 45-ml portion of diisopropylamide and 100 ml of dry THF were treated at 0 °C with 25.8 ml of 90% butyllithium and stirred for 0.5 at 0 °C. A mixture of 27 ml of hexamethylphosphoramide, 18.7 ml of freshly distilled hexanoic acid, and 45 ml of dry THF was added slowly at 0 °C to the stirred lithium diisopropylamide. After stirring for 6 h at 0 °C, 20 ml of D_2O was added slowly, and the mixture was stirred overnight, acidified to pH 5, and extracted with anhydrous Et_2O. Distillation of the residue after evaporation yielded 12.9 g of labeled product, bp 108–112 °C (15 mm). NMR indicated that this material was 42% α-d_1.

The acid was converted to acid chloride by conventional treatment with thionyl chloride. A solution of 6.5 g of labeled hexanoyl chloride in 15 ml of THF was added dropwise at 0 °C to a mixture of 5.1 g of hexylamine, 20 ml of THF, and 30 ml of 1% NaOH. The mixture was stirred for 10 h at room temperature, layers were separated, and the aqueous phase was extracted with ether. Work-up of the combined organic phases yielded 8.5 g of **9**, bp 135 °C (2.7 mm). Mass spectral analysis indicated that this material was 28% α-d_1. Compound **9** was irradiated in dioxane as previously described and the alcohols purified by preparative GLC. Deuterium incorporation was measured by comparing the (P + 1)/[P + (P + 1)] ratios for unlabeled alcohol **6** (0.092) vs. that obtained from irradiation of **9** (0.136).

Acknowledgment. This research was partially supported by a grant from the Center for Materials Research of the University of Maryland.

Registry No.—**1**, 10264-29-6; **4a**, 7501-79-3; **4b**, 57969-34-3; **4c**, 628-02-4; **4d**, 3418-05-1; **4e**, 628-62-6; **4f**, 79-05-0; **4g**, 10264-24-1; **7** isomer 1, 57969-35-4; **7** isomer 2, 57969-36-5; hexanal, 66-25-1.

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(10) The exchange conditions were essentially those used for a series of fatty acids. See P. E. Pfeffer and L. S. Silbert Abstracts, Middle Atlantic Regional Meeting of the American Chemical Society, Wilkes-Barre, Pa., April 23–26, 1974, paper no. 188.
(11) All photolysis reactions were accompanied by the formation of extensive amounts of polymeric materials. Irradiation of cyclohexane alone afforded small amounts of **8** as reported previously but no **9**, **10**, or **11**.
(12) The formations of these secondary products is predictably inefficient. For example, the photoreduction of acetone in dioxane[9a] affords the alcohol in only 16% yield. The addition product of 1-octene to dioxane is produced in 5% yield (27% when acetone sensitizer was employed).[13] In our hands irradiation of acetaldehyde in cyclohexane gave a 7% yield of **11** (by GLC).
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Cyclopropane Ring Opening with Pyridine Hydrochloride

Lucio Pellacani, Paolo A. Tardella,* and M. Antonietta Loreto

Istituto di Chimica Organica dell'Università di Roma, 00185 Roma, Italy

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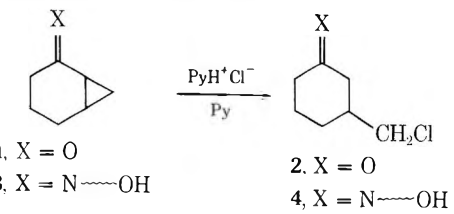
Two electron-withdrawing groups will make a cyclopropane derivative susceptible to suffer ring opening by nucleophilic attack[1-2], while monosubstituted cyclopropane rings require a strong nucleophile (like mercaptide ion[3]) or very strained systems.[4-6]

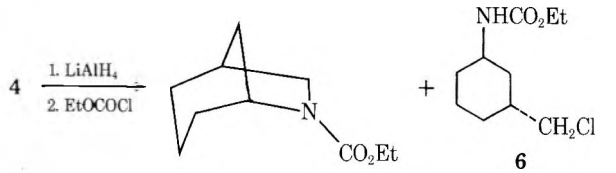
We have found that pyridine hydrochloride can produce the ring cleavage of bicyclo[4.1.0]heptan-2-one (**1**) and of its oximes **3**. When **1**[7] was refluxed in dry pyridine in the presence of pyridine hydrochloride for 20 h a high yield of 3-chloromethylcyclohexanone (**2**) was obtained.



1, X = O
3, X = N—OH
2, X = O
4, X = N—OH

Under the same conditions a syn and anti mixture of **3** furnished a syn and anti mixture of **4**. Traces of **2** were also found if the reaction medium was not perfectly dry. Interestingly, only **4** was obtained when the oximation of **1** was accomplished according to the usual procedure using hydroxylamine hydrochloride in ethanolic pyridine solution.

The structure of **4** was deduced from spectral data (ir, NMR, MS). Confirmatively *N*-carbethoxy-6-azabicyclo[3.2.1]octane (**5**) was recognized as one of the two products obtained by the lithium aluminum hydride reduction of **4** followed by treatment with ethyl chlorocarbonate; the other one was the chlorourethane **6**. An authentic sample of **5** was prepared from *m*-aminobenzoic acid according to the reported procedure.[8] **6** and its cis isomer were obtained also by catalytic hydrogenation of **4**.



5 6

We think that at least two features of the compounds **1** and **3** are determinant in the nucleophilic cyclopropane ring opening: the conjugation of the three-membered ring with a π system and the participation of the cyclopropane of a more strained system. According to this assumption bicyclo[4.1.0]heptane was recovered unchanged after an analogous treatment with pyridine hydrochloride in pyridine. In addition we found both cyclopropyl methyl ketone and its oximes to react quite slowly under the conditions used for the cleavage of **1** and **3**.

The peculiarity of pyridine hydrochloride[9] in such a hydrochloric acid addition to a cyclopropane ring appears clearly. Bicyclo[4.1.0]heptane was reported to react with 12 M HCl in equimolar ratio at room temperature. After 6 h a mixture of olefins and chlorides was obtained.[10] Actually we found that both **1** and **3** remained unreacted under the same conditions. However, α-cyclopropyl ketones are known to give ring cleavage in HBr–AcOH at room temperature.[11]

The ring opening is selective. The C_1–C_7 bond cleavage observed is consistent with a previous report according to which this bond is the weakest because of its large orbital overlap with the adjacent π system.[12] This selectivity, the high yield obtained, and the possibility of the hydroxyiminic function preservation can get this sequence of reactions regarded as a useful synthetic route to the azabicycloalkanes.

Experimental Section

General. GC analyses were performed on a Carlo Erba Fractovap GI gas chromatograph equipped with a column of Apiezon L (60 m × 0.25 mm) and on a Carlo Erba Fractovap GV gas chromatograph equipped with a column of 4% OV 17 (2 m × 3 mm). Infrared spectra were obtained on a Perkin-Elmer 257 Infracord instrument. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R32 90-MHz spectrometer, using Me_4Si as an internal standard. Mass spectra were obtained on an AEI-MS12 spectrometer at an ionization potential of 70 eV. GC–MS spectra were obtained using a column of 2% OV 17 (2 m × 2 mm).

Oximes of Bicyclo[4.1.0]heptan-2-one (3). A solution of 2.2 g (20 mmol) of 1,[7] 2.1 g (30 mmol) of hydroxylamine hydrochloride, and 3.2 g of $CH_3COONa{\cdot}3H_2O$ in 16 ml of ethanol was heated under reflux for 6 h. To the cooled mixture a saturated NaCl solution was added. Extraction with ether followed by evaporation afforded a residue of 1.9 g (76%) of **3**: mp 83–86 °C (petroleum ether); the GC analysis showed two partially overlapped peaks of similar areas, whose GC–MS spectra were nearly identical; ir (CCl_4) 3600, 3250, 3090, 3010 cm^{-1}; NMR (CCl_4) δ 0.4–1.1 (m, 3

H), 1.1–2.7 (m, 7 H), 8.5 (s, 1 H); MS *m/e* 125 (parent and base peak).

Treatment of 1 with Py·HCl in Py. A mixture of 1.75 g (16 mmol) of **1** and 3.7 g (32 mmol) of pyridine hydrochloride (freshly prepared[13]) in 40 ml of dry pyridine was refluxed during 20 h. After extraction, washing with saturated NaCl solution, drying, and evaporation of the organic phase, 1.76 g (76%) of **2** was obtained: bp 103–107 °C (15 mm);[14] ir (CCl_4) 1720 cm^{-1}; NMR (CCl_4) δ 3.45 (m, CH_2Cl); MS *m/e* 148 (isotopic), 146 (parent), 97 (base peak). Treatment of the crude ketone with hydroxylamine hydrochloride afforded exclusively **4**.

Treatment of 3 with Py·HCl in Py. As described above, 2.0 g (16 mmol) of **3** was treated with 3.7 g (32 mmol) of pyridine hydrochloride in 40 ml of pyridine to give 2.0 g (77%) of **4**: bp 80–85 °C (1 mm);[14] NMR (CCl_4) δ 3.45 (m, CH_2Cl); MS *m/e* 163 (isotopic), 161 (parent), 126 (base peak).

Treatment of Bicyclo[4.1.0]heptane, Cyclopropyl Methyl Ketone, and Cyclopropyl Methyl Ketone Oximes with Py·HCl in Py. The title compounds, obtained by WBL, Fluka, and according to a reported procedure,[15] respectively, were treated as above. NMR and GC analyses showed that none of them suffered a detectable transformation.

Treatment of 1 with NH_2OH·HCl in the Presence of Py. A mixture of 2.2 g (20 mmol) of **1** and 2.1 g (30 mmol) of hydroxylamine hydrochloride in 15 ml of ethanol and 15 ml of pyridine was refluxed for 3 h. Water was added and the solution was extracted with ether. Upon washing with 2 N HCl and water, drying, and evaporation of the organic phase 480 mg (15%) of **4** remained as a yellowish oil, purity 85% (GC); the remaining 15% was the ketone **2**.

Treatment of 2 and 4 with 12 M HCl. An equimolar mixture of **2** or **4** and 12 M HCl was shaken for 6 h at room temperature. After the usual work-up the GC and ir analyses showed only the presence of **2** or **4**, respectively.

$LiAlH_4$ Reduction of 4. A solution of 1.92 g (12 mmol) of **4** in 30 ml of anhydrous ethyl ether was added dropwise to a refluxing mixture of 1.8 g (48 mmol) of lithium aluminum hydride in 40 ml of ethyl ether. After 3 h of reflux, work-up, and treatment with ethyl chloroformate,[16] the GC of the urethanes mixture showed two peaks. The product with the shorter retention time (55%) was recognized as **5** on the basis of the GC and GC–MS comparison with an independently prepared sample,[8] MS *m/e* 183 (parent), 140 (base peak). The other product (45%) showed the same retention time and fragmentation pattern as the chlorourethane **6**, one of the two isomers obtained in the catalytic reduction of **4** (see below), MS *m/e* 221 (isotopic), 219 (parent), 90 (base peak).[17]

Catalytic Hydrogenation of 4. A solution of 2.1 g (13 mmol) of **4** in 13 ml of acetic acid (distilled on $KMnO_4$), 6 ml of water, and 2.2 ml of concentrated HCl was hydrogenated at 50 psi at room temperature for 20 h in the presence of 150 mg of PtO_2. The filtrate was extracted and the crude product was treated with ethyl chloroformate[16] to afford 1.96 g (69%) of a 57:43 mixture of **6** and its cis isomer: bp 135–140 °C (1 mm);[14] ir (CCl_4) 3450, 1725 cm^{-1}; NMR (CCl_4) δ 1.2 (t, CH_3 of Et), 4.0 (q, CH_2 of Et), 4.6 (broad, NH), 3.35 (m, CH_2Cl); MS *m/e* 221 (isotopic), 219 (parent), 90 (base peak).[17] If the crude product of hydrogenation was made alkaline and allowed to stand at room temperature for several hours before the treatment with ethyl chloroformate, only **5** and **6** were detected.

Acknowledgment. National Research Council (CNR) Rome is gratefully acknowledged for partial financial support and Mr. A. Santi for mass spectra recording.

Registry No.—**1**, 5771-58-4; **2**, 57719-96-7; *syn*-**3**, 57719-97-8; *anti*-**3**, 57719-98-9; *syn*-**4**, 57719-99-0; *anti*-**4**, 57720-00-0; **5**, 57720-01-0; **6**, 57720-02-2; **6**, cis isomer, 57720-03-3; hydroxylamine hydrochloride, 5470-11-1; pyridine hydrochloride, 628-13-7; lithium aluminum hydride, 16853-84-3.

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A New Method for the Synthesis of Biscyclododecylidene Cycloalkylidene Triperoxides

K. Paul,* P. R. Story, P. Busch, and J. R. Sanderson

Department of Chemistry, The University of Georgia, Athens, Georgia 30602

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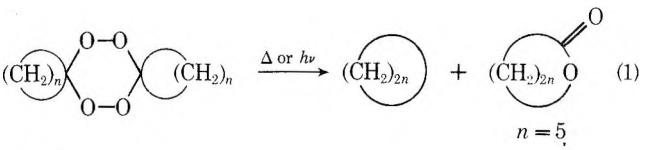
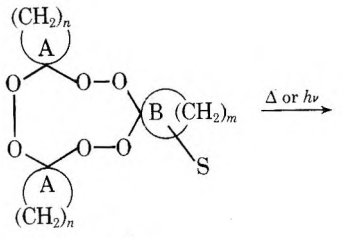
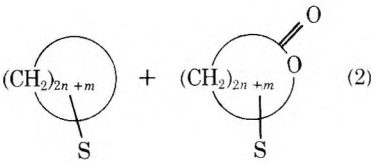
Story and co-workers[1] discovered that the thermal and photochemical decomposition of cyclic ketone peroxides produces macrocyclic lactones and hydrocarbons. This can be illustrated by eq 1 and 2.



(1)



II



(2)

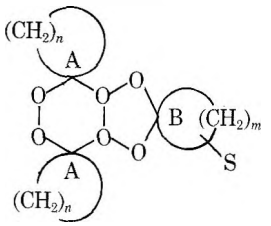
Easy access to the appropriate precursor peroxides constitutes a key step for the synthesis of the desired macrocyclic compounds. Availability of peroxides of type II where $n \neq m$ will obviously broaden the scope of the reaction in terms of varying the size and introduction of the desired functionality in the macrocyclic ring.

A limited number of mixed peroxides of type II have earlier been synthesized by Criegee[2] and the process has been extended by Oldekop[3] and co-workers. Story and co-workers[4] also utilized Criegee's[2] procedure for synthesizing several mixed peroxides. Criegee's procedure essentially consists of treating 1,1′-dihydroperoxydicycloalkyl peroxide with an excess of the appropriate ketone in the presence of anhydrous $CuSO_4$ (eq 3) over an extended reaction period of 1–2 weeks.

Criegee's procedure suffers from the drawback that it

* Address correspondence to Story Chemical Corp., Muskegon, Mich. 49445.

Table I. List of New Cyclic Trimeric Peroxides



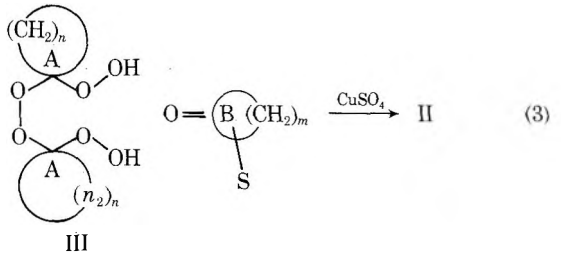
Compd		% yield[a]	Mp, °C	Anal.,[c,d] % Calcd	Found
1	$n = 11, m = 4$	55	178–181 dec	C 70.12 H 10.55	C 69.68 H 10.49
2	$n = 11, m = 5$	30	160–162 dec	C 70.55 H 10.66	C 69.17 H 10.56
3	$n = 11, m = 6$	64	188–190	C 70.95 H 10.66	C 69.89 H 10.99
4	$n = 11, m = 7$	42	185–187	C 71.33 H 10.85	C 70.93 H 10.71
5	$n = 11, m = 10$	10	197–198	C 72.37 H 11.11	C 72.39 H 11.19
6	$n = 11, m = 14$	27	179–183	C 73.54 H 11.39	C 73.77 H 11.53
7	$n = 11, m = 5$	28	141–143	C 70.95 H 10.76	C 70.46 H 10.89
8	$n = 11, m = 5$ S = 4-Me	31	157–161	C 70.95 H 10.76	C 71.39 H 10.71
9	$n = 11, m = 5$ S = 4-Et	27	150–153	C 71.38 H 10.85	C 71.74 H 10.96
10	$n = 11, m = 5$ S = 4-*tert*-butyl	22	157–161 dec	C 72.04 H 11.02	C 72.32 H 11.22
11	$n = 11, m = 5$ S = 4-MeO	15	164–167	C 68.85 H 10.63	C 68.85 H 10.44
12	$n = 11$ B = 2-adamantanone	20	178–180	C 72.56 H 10.39	C 72.01 H 10.49

[a] Yields were not optimized. [b] The peroxides were recrystallized from ethyl acetate–chloroform. [c] Analysis performed by Atlantic Microlab, Inc., Atlanta, Ga. [d] Supplementary ir and NMR data.

Table II. Yield of Macrocyclic Hydrocarbons and Lactones

Peroxide	Hydrocarbon	Yield, %[a] hydrocarbon	Lactone	% yield lactone
$n = 11, m = 4$	Cyclohexacosane	36	Cycloheptacosanolide	14
$n = 11, m = 5$	Cycloheptacosane	34.7	Cyclooctacosanolide	12.3
$n = 11, m = 6$	Cyclooctacosane	30.0	Cyclononacosanolide	12.2
$n = 11, m = 7$	Cyclononacosane	Undetermined	Cyclotriacontanolide	Undetermined

[a] Yields are GC yield. Detailed procedures for the indentification of products and yield determinations are given in ref 7.



III (3)

does not permit the use of solid ketone. Moreover, when Criegee's procedure was used for the synthesis of biscyclododecylidene cyclohexylidene triperoxide (II, $n = 11$, $m = 5$) no detectable amount of the desired product was found even after 3 weeks.

We have developed a simple procedure for the synthesis of biscyclododecylidene cycloalkylidene triperoxides. Table I lists the peroxides synthesized by this procedure. Our procedure essentially consists of slow addition of a solution of 1,1′-dihydroperoxydicyclododecyl peroxide to a solution of the appropriate ketone in the presence of an acid catalyst. A few of the synthesized peroxides ($n = 11$, $m = 4$, 5, 6, 7) were thermolyzed and the products identified by ir and mass spectrometry. Yields of the hydrocarbons and lactones are given in Table II.

This new procedure gives access to a series of mixed triperoxides of type II unknown before and hence to the possibility of synthesizing large-ring compounds which could be synthesized only with difficulty by conventional procedures.[5]

Experimental Section

1,1′-Dihydroperoxydicyclododecyl Peroxide (III, $n = 11$). To a cold (−20 °C) solution of 26.8 g (0.12 mol) of 1,1-dihydroperoxycyclododecane[6] in 550 ml of propionic acid, 7.5 ml of 10% $HClO_4$ in glacial acetic acid was added with stirring. After 1 h at −20 °C, the reaction mixture was maintained at 0 °C overnight. Solid product was filtered off and thoroughly washed with water. Recrystallization from PhH produced pure compounds in 80% yield, mp 151–152 °C (exploded).

Anal. Calcd for $C_{24}H_{46}O_6$: C, 67.0; H, 10.7. Found: C, 67.03; H, 10.7.

Infrared (KBr) 3400 (vs), 2940 (vs, sh at 2850), 1470 (vs, sh at 1445), 1415 (vw), 1385 (m-s, sh at 1350), 1322 (vw), 1300 (vw), 1280 (w), 1260 (m, sh at 1245), 1218 (w), 1190 (vw), 1155 (s, sh at 1170), 1055 (s, sh at 1065 and 1070), 995 (m-s, sh at 1010 and 982), 945 (m-s), 905 (m-w), 870 (m), 855 (w), 840 (vw), 820 (m-w), 795 (m), 740 (m), 710 cm^{-1} (m).

General Procedure for the Preparation of Biscyclododecylidene Cycloalkylidene Triperoxides. To a cold (5–10 °C), vigorously stirred solution of the ketone (100 mmol) in 20–25 ml of PhH containing 30 drops of 10% $HClO_4$ in glacial acetic acid, a $CHCl_3$ solution (1 g, 50 ml) of 1,1′-dihydroperoxydicyclododecyl peroxide was added from a buret (approximately 1 ml/min). After an additional 30–72 h in the cold, most of the solvent was removed at room temperature. On trituration of the residue with methanol, solid material appeared. Filteration and recrystallization from a 2:3 mixture of CH_3COOEt and $CHCl_3$ gave the desired product in reasonably pure condition.

Thermolysis of the Peroxide. Details of the procedure for pyrolysis and identification of the products of pyrolysis are given in the earlier papers.[7]

Ir and NMR Data for Compounds 1–12 (See Table I). Compound 1. Infrared (CCl_4) 2933 (vs), 2860 (w), 2850 (s), 1470 (vs), 1448 (s), 1370 (vw), 1350 (w), 1300 (vw), 1285 (w), 1250 (m), 1220 (m), 1205 (vw), 1192 (w), 1178 (m), 1160 (vw) 1110 (vw), 1080 (s), 1069 (s), 1010 (s), 992 (w), 980 (vw), 955 (m), 915 (w), 880 cm^{-1} (m).

Compound 2. NMR ($CDCl_3$, Me_4Si) δ 1.28 (singlet, sharp) 1.53 (shoulder, broad); Infrared (CCl_4) 2925 (vs), 2860 (vw), 2850 (s), 1470 (vs), 1448 (s), 1360 (w), 1335 (vw), 1325 (w), 1300 (vw), 1285 (vw), 1278 (m), 1265 (vw), 1250 (m), 1220 (m), 1205 (vw), 1192 (vw), 1178 (m), 1170 (m), 1160 (w), 1250 (vw), 1110 (vw), 1092 (w), 1070 (s), 1010 (s), 995 (w), 970 (w), 952 (m), 915 (m), 880 cm^{-1} (m). (m).

Compounds 3. Infrared (CCl_4) 2925 (vs), 2860 (w), 2850 (s), 1470 (vw), 1450 (s), 1370 (w), 1325 (w), 1300 (vw), 1285 (w), 1250 (m), 1220 (m), 1210 (vw), 1195 (vw), 1175 (m), 1160 (vw), 1110 (w), 1080 (v 1078 (s), 1040 (vw), 1015 (s), 970 (vw), 955 (w), 915 (w), 880 cm^{-1} (m).

Compound 4. Infrared (CCl_4) 2925 (vs), 2850 (s, sh at 2860), 1472 (vs), 1448 (s), 1370 (vw), 1352 (w), 1325 (w), 1300 (w), 1285 (w), 1270 (vw), 1250 (m), 1235 (vw), 1220 (m), 1195 (vw), 1178 (m), 1160 (w), 1124 (w), 1110 (w), 1095 (vw), 1070 (s), 1010 (s), 995 (m), 925 (m), 905 (m), 915 (m), 880 cm^{-1} (m).

Compound 5. NMR ($CDCl_3$, Me_4Si) δ 1.37 (shoulder, sharp), 1.50 (shoulder, broad); infrared (CCl_4) 2930 (vs), 2865 (s), 1470 (s), 1440 (s), 1330 (vw), 1255 (m), 1228 (m), 1115 (vw), 1075 (s), 1015 (s), 960 (m), 920 (m), 880 cm^{-1} (m).

Compound 6. NMR ($CDCl_3$, Me_4Si) δ 1.27 (singlet, sharp); infrared (CCl_4) 2930 (vs), 2860 (s), 1468 (s), 1445 (s), 1365 (vw), 13 (vw), 1320 (w), 1245 (m), 1218 (m), 1175 (w), 1165 (m), 1080 (w), 1065 (s), 1005 (s), 968 (w), 950 (m), 910 (w), 870 cm^{-1} (m).

Compound 7. NMR ($CDCl_3$, Me_4Si) δ 0.88, 1.02 (doublet, sharp) 1.23 (singlet, sharp), 1.48 (shoulder, broad); infrared (CCl_4) 2930 (vs), 2860 (s), 1468 (s), 1445 (s), 1365 (vw) 1345 (vw), 1320 (w), 1245 (m), 1218 (m), 1175 (w), 1165 (m), 1105 (vw), 1080 (w), 1065 (s), 1005 (s), 968 (w), 950 (m), 910 (w), 870 cm^{-1} (m).

Compound 8. NMR ($CDCl_3$, Me_4Si) δ 0.82, 0.90 (doublet?, broad), 1.28 (singlet, sharp) 1.52 (shoulder, broad); infrared (CCl_4) 2930 (vs), 2850 (s), 1470 (s), 1445 (s), 1365 (vw), 1350 (w), 1290 (vw), 1250 (m), 1220 (w), 1190 (vw), 1165 (s), 1150 (m), 1078 (vw), 1062 (s), 1045 (w), 1010 (s), 990 (w), 980 (w), 950 (m), 910 (w), 900 (w), 870 cm^{-1} (m).

Compound 9. NMR ($CDCl_3$, Me_4Si) δ 0.80 (singlet, broad), 0.90 (singlet, broad) 1.28 (singlet, sharp), 1.52 (shoulder, broad); infrared (CCl_4) 2930 (vw), 2855 (s), 1470 (s), 1445 (s), 1350 (w), 1325 (w), 1280 (vw), 1245 (w), 1190 (w), 1165 (s), 1110 (w), 1080 (vw), 1062 (s), 1065 (m), 990 (vw), 970 (w), 950 (s), 905 (vw), 870 cm^{-1} (m).

Compound 10. NMR ($CDCl_3$, Me_4Si) δ 0.80 (singlet, sharp), 1.22 (singlet, sharp), 1.50 (shoulder, broad); infrared (CCl_4), 2940 (vs), 2860 (s), 1470 (s), 1445 (m-s), 1365 (m), 1350 (vw), 1320 (vw), 1280 (w), 1240 (w), 1215 (w), 1190 (w), 1172 (w), 1155 (w), 1065 (s), 1005 (m, sh at 990), 950 (m-w, sh at 930), 910 (m-w), 872 (m-w).

Compound 11. NMR ($CDCl_3$, Me_4Si) δ 1.23 (singlet, sharp), 1.50 (shoulder, broad), 3.11 (singlet, sharp); infrared (CCl_4) 2430 (vs), 2860 (s), 2820 (vw), 1470 (vs), 1450 (s), 1370 (w), 1350 (vw), 1325 (w), 1280 (w), 1245 (m), 1320 (w), 1190 (vw), 1175 (vw), 1160 (m), 1145 (w), 1105 (s), 1100 (s), 1080 (vw), 1065 (vs), 1005 (m), 990 (w), 965 (w), 950 (m), 915 (m), 872 cm^{-1} (m).

Compound 12. NMR ($CDCl_3$, Me_4Si) δ 1.23 (singlet, sharp), 1.40–2.30 (complex); infrared (CCl_4) 2930 (vs), 2860 (s), 1470 (s), 1450 (s), 1320 (w), 1285 (w), 1110 (s), 1065 (s), 1015 (s), 1000 (s), 960 (m), 925 (m), 970 cm^{-1} (m).

Registry No.—**1**, 36079-74-0; **2**, 33525-84-7; **3**, 36079-75-1; **4**, 53783-78-1; **5**, 57951-51-6; **6**, 57951-52-7; **7**, 53783-75-8; **8**, 53783-73-6; **9**, 53783-72-5; **10**, 53783-71-4; **11**, 32616-65-2; **12**, 57951-53-8; III (n = 11), 50782-53-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cycloundecanone, 878-13-7; cyclopentadecanone, 502-72-7; 2-methylcyclohexanone, 583-60-8; 4-methylcyclohexanone, 589-92-4; 4-ethylcyclohexanone, 5441-51-0; 4-*tert*-butylcyclohexanone, 98-53-3; 4-methoxycyclohexanone, 13482-23-0; 2-adamantanone, 700-58-3; cyclohaxacosane, 297-16-5; cycloheptacosane, 297-23-4; cyclooctacosane, 297-24-5; cycloheptacosanolide, 57951-54-9; cyclooctacosanolide, 57951-55-0; cyclononacosanolide, 57951-56-1.

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Bromination of Nitroalkanes with Alkyl Hypobromites

Victor L. Heasley,* Don R. Titterington, and Tracy L. Rold

Department of Chemistry, Point Loma College, San Diego, California 92106

Gene E. Heasley

Department of Chemistry, Bethany Nazarene College, Bethany, Oklahoma 73008

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Recently we reported that methyl hypobromite adds to olefins by an ionic mechanism if the solvent is polar, such as methylene chloride, and in the presence of a radical inhibitor.[1] In another publication we showed that alkyl hypochlorites react with olefins in nitromethane by chlorinating the solvent to give chloronitromethane rather than adding to the olefin.[2] In this reaction the olefin functions as a catalyst. Certain aromatics also catalyze chlorination of nitromethane (naphthalene and the xylenes) while other aromatics react with alkyl hypochlorites in nitromethane to give chloroaromatics.[3]

On the basis of these observations we became interested in determining what type of reaction would occur when alkyl hypobromites are added to olefins in nitromethane. Methyl hypobromite could add to the olefin as occurred with the less polar solvent methylene chloride, or bromonitromethane might be the product, by analogy with the reaction of alkyl hypochlorites in nitromethane. Finally, we considered that it was possible that the polar solvent nitromethane might cause even *tert*-butyl hypobromite to add to olefins by an ionic mechanism.

When *tert*-butyl hypobromite was added to 1-hexene in nitromethane we were surprised to find that in addition to bromonitromethane (**1**), dibromonitromethane (**2**) and tribromonitromethane (**3**) were also formed.

$$CH_2{=}CH(CH_2)_3CH_3 + (CH_3)_3COBr \xrightarrow{CH_3NO_2} \underset{\mathbf{1}}{BrCH_2NO_2} + \underset{\mathbf{2}}{Br_2CHNO_2} + \underset{\mathbf{3}}{Br_3CNO_2} + (CH_3)_3COH$$

The catalytic role of the olefin, 1-hexene, was established by the fact that no reaction occurred between *tert*-butyl

hypobromite and nitromethane unless 1-hexene was present. We tried several other olefins, such as 1-butene, 1-propene, styrene, cyclohexene, α-methylstyrene, and 1,2-dichloroethylene, and all of them functioned as catalysts except 1,2-dichloroethylene, which has strong electron-withdrawing groups. The relative amounts of **1**, **2**, and **3** did not depend on the structure of the olefin.

The amounts of **1**, **2** and **3** that are formed depend on the method of addition. For example, if *tert*-butyl hypobromite is added instantly to a solution of 1-hexene in nitromethane the products are formed in the following amounts (yield, 85%); **1** (68%), **2** (10%), and **3** (22%). On the other hand, if the hypobromite is added dropwise the following product mixture is formed (yield, 88%): **1** (24%), **2** (5%), and **3** (71%). Furthermore, when the dropwise addition was followed by VPC, we observed that initially **1** is formed, but as more hypobromite is added increasing amounts of **2** and **3** are formed. The concentrations of **1** and **2** soon reach a constant level and addition of more hypobromite results in formation of **3**. These results suggest that **3** is formed from **2**, and **2** in turn is formed from **1**, and that there is an increase in reactivity toward the hypobromite in the order of $2 > 1 > CH_3NO_2$. In a separate experiment we established that **2** reacts with *tert*-butyl hypobromite to give **3**. Using the two different addition procedures and an appropriate olefin as a catalyst offers a unique method for synthesizing large quantities of **1** or **3**: the olefin can be removed very easily if it is low boiling (1-butene); the reactions are "clean", with very few by-products; **1** can be made in large quantities simply by carrying out the rapid addition procedure on a large scale; large quantities of **3** can be produced by adding the alkyl hypobromite dropwise to the nitromethane-olefin solution until most of the nitromethane has been converted to **3**; and the **1** and **3** can be separated easily by distillation, since both are relatively free of the other. Methyl hypobromite also reacted with olefins in nitromethane to give results which were essentially identical with those of *tert*-butyl hypobromite.

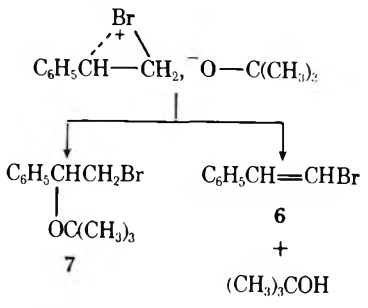
A careful study was made on the addition of *tert*-butyl hypobromite to styrene in nitroethane (rapid addition, see the following equation) to determine whether addition of hypobromite to the double bond of styrene had occurred.

$$C_6H_5CH{=}CH_2 + (CH_3)_3COBr \xrightarrow{CH_3CH_2NO_2} CH_3CHNO_2 + \underset{\displaystyle Br}{\overset{\displaystyle Br}{\underset{|}{\overset{|}{CH_2{-}C{-}NO_2}}}} + (CH_3)_3COH$$

4 **5**

Besides **4** (50%) and **5** (18%), small amounts of β-bromostyrene (**6**, <1%) and the ionic addition product 2-bromo-1-*tert*-butoxy-1-phenylethane (**7**, 5%) were also detected.[4] Apparently **6** and **7** are formed by the following mechanism:

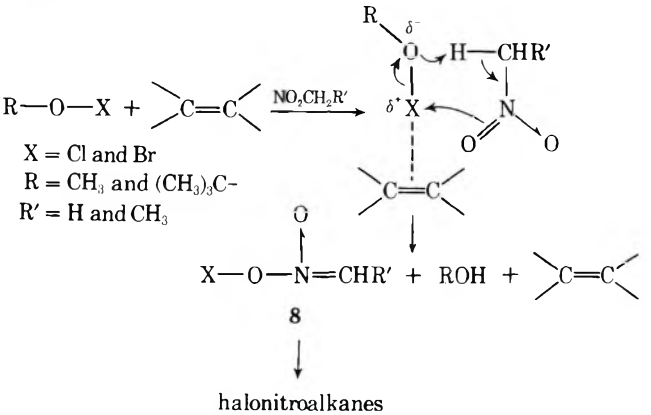
$$C_6H_5CH{=}CH_2 + (CH_3)_3OBr \xrightarrow{CH_3CH_2NO_2}$$



Dibromostyrene (15%) was also formed in the above reaction. In fact, we always observe the formation of dibromides when alkyl hypobromites are allowed to react with olefins, even when no bromine was detectable in the hypobromite solution. We have no explanation for their formation.[6] An analogous study on the addition of *tert*-butyl hypobromite to styrene in nitromethane gave approximately the same amount of addition product (**7**); of course, **1**, **2**, and **3** were also formed. We anticipated an increase in the amount of **6** and **7** in nitromethane since it is more polar than nitroethane but this did not occur. Methyl hypobromite reacted with styrene in nitromethane and nitroethane to give similar amounts of substitution (β-bromostyrene) and addition (2-bromo-1-methoxy-1-phenylethane) products to that of *tert*-butyl hypobromite.

The one striking difference between the reactions of alkyl hypobromites and hypochlorites with olefins in nitromethane involves the formation of tribromonitromethane (**3**). Under no conditions was the formation of trichloronitromethane (Cl_3CNO_2) observed even when *tert*-butyl hypochlorite was added dropwise until a very concentrated solution of chloronitromethane ($ClCH_2NO_2$) was formed. Apparently the reactivity of chloronitromethane toward hypochlorite is not greater than nitromethane itself (it may even be less reactive). The order of reactivity of $2 > 1 > CH_3NO_2$ would appear to follow the expected acidities of the hydrogens in the bromonitromethanes (**1** and **2**). However, if the acidities of the hydrogens in **1** and **2** do account for the order of reactivity with the bromonitromethanes we have no explanation why this also should not be a factor in the chloronitromethanes since the same order of acidities would be expected here.

Although we are uncertain of the mechanisms in the reactions of alkyl hypohalites with olefins in nitromethane, these reactions (alkyl hypochlorites and hypobromites) do appear to have several areas in common. Both react with olefins in nitroalkanes in the presence of the radical inhibitor oxygen, suggesting that ionic reactions are involved; and the rates of reaction of both hypohalites are dependent on the basicity of the olefins. Taking into consideration these similarities and the catalytic role of the olefin, the mechanism is probably best described as we did previously with hypochlorites,[2] and modified here to include the hypobromites:



An explanation for the difference in product formation between rapid and slow addition may involve the fact that the reaction between nitromethane, hypobromite, and the olefin to give **8** (where R′ = H) is considerably more rapid than decomposition of **8** to **1**. Therefore, under the conditions of rapid addition most of the hypobromite would be converted to **8** before a substantial amount of monobromonitromethane (**1**) was formed. Consequently, the simultaneous concentrations of hypobromite and **1** would be low

and little dibromonitromethane (2) would be formed. In the case of slow addition there would be ample time for 8 to give 1 and the hypobromite would preferentially react with the more reactive 1 than nitromethane.[7]

Experimental Section

Reaction Conditions. To a stirred solution of 0.004 mol of olefin in 11.2 ml of nitroalkane maintained at ice-bath temperatures was added 2 ml (1.2 M) of *tert*-butyl hypobromite–carbon tetrachloride solution. (The concentrations of the alkyl hypobromites solutions varied somewhat depending on the preparation.) The reactions were essentially instantaneous but stirring was continued for a short time. Slow addition of the hypobromite was done with a dropping funnel or a dropping pipet. Rapid addition simply involved letting the hypobromite solution run in directly from a volumetric pipet. The reaction products were analyzed directly by VPC. The synthesis of methyl hypobromite has been described previously;[1] we used this same procedure to make *tert*-butyl hypobromite. As was the case with the alkyl hypochlorites, no reaction occurred between the alkyl hypobromites and the nitroalkanes unless the olefins were present.

Identification of Products. Bromonitromethane (1) and tribromonitromethane (3) were synthesized unambiguously by addition of the appropriate amount of bromine to a solution of nitromethane and base, and were identified by comparison of their infrared spectra with the reported spectra for these compounds.[8] Dibromonitromethane (2) was prepared as described for 1 and 3, and its structure was confirmed from its infrared spectrum (absorption bands, cm^{-1}), C–H, 2400; $-NO_2$, 1325 and 1575; C–Br, 600 and 675; and from its boiling point; reported,[9] 58–60 °C (13 mm) [175 °C (760 mm)]; found, 50 °C (5.5 mm) [180 °C (760 mm)]. 1-Bromonitroethane (4) and 1,1-dibromonitroethane (5) were synthesized unambiguously as previously described.[10] The ir spectrum of 4 also compared favorably with the reported spectrum.[7] The compound responsible for peak 4 was isolated from the reaction product (hypobromite, olefin, and nitroethane) by preparative VPC; the ir spectrum of the collected compound was identical with that of the unambiguously synthesized 4, with the exception of a small carbonyl absorption (contaminant) in the later. Compounds 1, 2, 3, and 5 were confirmed as products by comparisons of the retention times of the peaks assigned to them with the retention times of the authentic compounds. Styrene dibromide was prepared by addition of bromine to styrene. β-Bromostyrene was synthesized unambiguously by the decarboxylation of 2,3-dibromocinnamic acid.[11] The synthesis of 2-bromo-1-methoxy-1-phenylethane has been described previously.[12] 2-Bromo-1-*tert*-butoxy-1-phenylethane was isolated by preparative VPC and identified by its NMR spectrum:[13] δ 1.20 [s, 9, $C(CH_3)_3$], 3.35 (d, 2, CH_2), 4.65 (t, 1, CH), 7.35 (s, 5, C_6H_5).

Analysis Procedure. Compounds 1, 2, and 3 were separated on a 4 ft × 0.25 in. column packed with 2% DNP on Chromosorb W (60/80 mesh) DCMS at 65 °C (flow rate 60 ml/min He); under these conditions the retention times (min) were respectively 3.3, 6.5, and 13.0. The internal standard was *p*-bromochlorobenzene. Compounds 4 and 5 were separated as described for the bromonitromethanes with the exception that the column was 8 ft; the retention times (min) were respectively 4.8 and 9.1. The internal standard was *o*-bromotoluene. Compounds 6, 7, 2-bromo-1-methoxy-1-phenylethane, and styrene dibromide were separated on the same column as used for the bromonitromethanes (column temperature 100 °C) with the following retention times (min), respectively: 4.6, 11.7, 6.9, and 15.8.

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Registry No.—1, 563-70-2; 2, 598-91-4; 3, 464-10-8; 4, 563-97-3; 5, 7119-88-2; 6, 103-64-0; 7, 57951-57-2; nitromethane, 75-52-5; nitroethane, 79-24-3; methyl hypobromite, 28078-73-1; *tert*-butyl hypobromite, 1611-82-1; styrene dibromide, 7436-90-0; bromine, 7726-95-6; styrene, 100-42-5; 2-bromo-1-methoxy-1-phenylethane, 13685-00-2.

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(4) For a discussion of the role of olefins as catalysis in the reactions of alkyl hypochlorites with nitromethane, see ref 2.
(5) It is conceivable that the addition product could result from addition of Br_2 (formed by decomposition of the alkyl hypobromite) to styrene in the presence of *tert*-butyl alcohol (from the reaction of hypobromite with nitroethane) or by solvolysis of styrene dibromide in the presence of *tert*-butyl alcohol. We eliminated these possibilites by bromination of styrene in a mixture of nitroethane–*tert*-butyl alcohol and by solvolysis of styrene dibromide in the same solution, and determining that no addition product was formed.
(6) In our earlier study[1] on the addition of alkyl hypobromites to 1-hexene and styrene in dichloromethane, we also observed dibromide formation. At that time, we absolutely confirmed, using ultraviolet spectroscopy, that no more than a trace of molecular bromine was present in the hypobromite solutions. In the present study, more dibromides were formed when oxygen was passed through the reaction solution.
(7) At the moment of addition the concentration of hypobromite is high with rapid addition. It is conceivable that under these conditions the reaction occurs by a mechanism which is second order in hypobromite involving an anion of the structure $(R-O-Br-O-R)^-$; this would be analogous to bromination with molecular bromine in which the tribromide ion (Br_3^-) is involved. However, at this time we see no way of accounting for the difference in products between the two methods of addition on the basis of the structure of the anion.
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(13) The corresponding radical addition product (1-bromo-2-*tert*-butoxy-1-phenylethane) was prepared as described by Walling et al. [*J. Am. Chem. Soc.*, **87**, 1715 (1965)] and its spectrum was compared with that of 7. The spectra were essentially identical except for differences in chemical shifts.

Chlorination of Cyclopentadiene and 1,3-Cyclohexadiene with Iodobenzene Dichloride and Trichloramine

Victor L. Heasley,* Kerry D. Rold, and David B. McKee

Department of Chemistry, Point Loma College, San Diego, California 92106

Gene E. Heasley

Department of Chemistry, Bethany Nazarene College, Bethany, Oklahoma 73008

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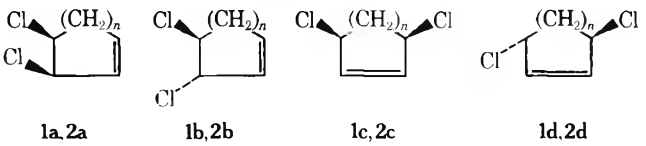
It has recently been shown that trichloramine reacts with olefins to give vicinal dichlorides by a radical mechanism,[1] and that iodobenzene dichloride and olefins also form vicinal dichlorides by either an ionic or radical mechanism depending on the conditions.[2] Since we had recently established the structures of the stereoisomeric dichlorides that result from chlorination of cyclopentadiene (1)[3] and 1,3-cyclohexadiene (2),[4] we felt that it would be of interest to



1a,2a 1b,2b 1c,2c 1d,2d

compare the product ratios from these chlorinating agents with those from molecular chlorine with the object being to obtain information on the bonding in the intermediate radicals and ion pairs. The products from reaction of the dienes with antimony pentachloride are also included for comparison purposes.[5]

The structures of the dichloride products are shown

Table I. Chlorinations of Cyclopentadiene and 1,3-Cyclohexadiene

Entry	Chlorinating agent	Solvent	Dichlorides, % 1a	1b	1c	1d	2a	2b	2c	2d	Yield, % 1	2
1	Cl_2	CH_2Cl_2	38	25	18	9	14	58	21	7	52	38
2	Cl_2	CCl_4	27	23	39	11	8	22	69	1	60	28
3	Cl_2	C_5H_{12}	13	29	29	28	15	49	33	3	68	34
4[a]	Cl_2	Neat	25	26	34	15					40	
5[b]	$PhICl_2$	CH_2Cl_2	10	17	24	49	3	39	18	40	43	67
6[b]	$PhICl_2$	CCl_4	5	21	41	33	<1	24	28	45	55	96
7[b]	$PhICl_2$	C_5H_{12}	7	17	44	32	3	36	28	32	74	74
8[a,c]	$PhICl_2$	CH_2Cl_2	1	44	29	26	0	46	10	44	85	90
9[a]	$PhICl_2$	Neat	0	41	30	29	1	49	9	41	59	88
10	NCl_3	CH_2Cl_2	19	37	26	18	9	47	20	24	54	99
11	NCl_3	CCl_4	14	36	26	24	8	41	31	20	71	92
12[b]	NCl_3	CCl_4	11	38	25	26						
13	NCl_3	C_5H_{12}	12	33	25	30	9	45	23	23	68	99
14[a]	NCl_3	Neat	12	38	25	25	6	46	19	29	55	58
15	$SbCl_5$	CH_2Cl_2	7	12	52	29					27	
16	$SbCl_5$	CCl_4	6	22	38	34	2	40	16	42	96	65
17	$SbCl_5$	C_5H_{12}	19	21	27	33					71	

[a] The reactants were illuminated with ultraviolet light and flushed with N_2. [b] 2,6-Dimethyl-4-*tert*-butylphenol was added (1 M) as an inhibitor. [c] The solution was 0.5 mol fraction in diene.

below where n = 1 and 2 for cyclopentadiene (**1**) and 1,3-cyclohexadiene (**2**), respectively.

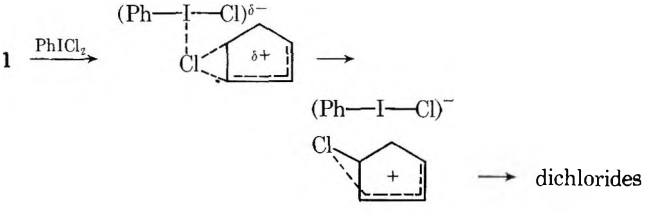
The amounts of the products and the corresponding reaction conditions are summarized in Table I. The following general observations can be made: (a) all three chlorinating agents give more trans 1,4-dichlorides than does molecular chlorine—this is particularly dramatic with 1,3-cyclohexadiene; (b) in most cases there is a decrease in amount of cis 1,2 addition with all of the chlorinating agents which is most notable with iodobenzene dichloride; and (c) the yields of the dichlorides (**2a–d**) from 1,3-cyclohexadiene are greatly improved with iodobenzene dichloride, trichloramine, and antimony pentachloride.

Entry 14 describes reaction conditions which are most conducive to a radical reaction: pure diene (molecule-induced homolysis); absence of an inhibitor (O_2 removed by N_2); and ultraviolet illumination. Product ratios (entries 10–13) under all of the different reaction conditions are essentially identical with those from entry 14, suggesting that trichloramine reacts with dienes **1** and **2** only by a radical mechanism.[6] The intermediate radical (**3**) apparently has

3

little bridging between the chlorine and the adjacent allylic system since trichloramine does give considerable cis 1,2 addition. The electron density in **3** may be somewhat lower at C_3, and hence less stable and more reactive, since trans 1,2-dichloride **1b** is the major product under radical conditions, or the product ratios from the reaction of radical intermediate **3** with the chain-carrying species (NCl_3, NCl_2, NCl, etc.) simply may reflect a steric preference.[7] If chlorine reacts with cyclopentadiene (**1**) by a radical mechanism (entry 14),[8] the radical intermediate from molecular chlorine should be identical with **3** from trichloramine, but since the product ratios are different the intermediate must exhibit a steric preference in its reaction with the different chlorine donors. This is further exemplified by iodobenzene dichloride, which, under radical conditions (entry 9), shows similar reactivity to trichloramine except for the fact that it gives little cis 1,2 addition to either dienes **1** or **2**. Apparently the large iodobenzene dichloride molecule experiences severe steric hindrance as it approaches C_3 (cis) in both of the intermediate radicals. The radical intermediate from 1,3-cyclohexadiene also shows a slight preference for trans attack at C_3 in the chain-propagating step with both trichloramine and iodobenzene dichloride (entries 10–14 and 8–9, respectively).

We feel that a comparison of the ionic addition products from the reaction of iodobenzene dichloride (entries 5, 6, and 7)[9,10] and chlorine (1, 2, and 3) with dienes **1** and **2** raises an interesting question concerning the structure of the ion pair from iodobenzene dichloride. The results in Table I show that iodobenzene dichloride gives considerably more trans 1,4 addition to both **1** and **2** than does molecular chlorine. We suggest that this difference can be explained on the basis of a consideration of the respective ion pairs. In the reaction of iodobenzene dichloride the ion pair (**4**, shown with diene **1**)[11] would involve the large anion ($Ph–I–Cl^-$) which would experience steric hindrance as it



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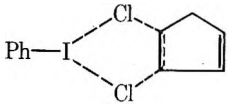
approached C_3 in a cis direction (cis 1,2 addition), but could undergo trans attack freely at the same carbon. On the other hand, the small chloride ion in the corresponding ion pair from molecular chlorine apparently experiences little steric hindrance during attack at any of the positions. Steric hindrance also appears to be involved in cis attack of the large anion at C_1 since there is a significant reduction in cis 1,4 addition for both dienes in going from chlorine to iodobenzene dichloride; this is particularly dramatic for diene **2**. (The results for diene **1** in pentane are, for unknown causes, exceptions to these comparisons.) Tanner and Gidley[2] do not discuss the structure of the anion in the ion pair but show chloride ion and the iodobenzene molecule in their ion pair. It is conceivable that our results could be explained on the basis that the chloride ion and the iodobenzene molecule remain in close proximity in the ion pair and that the large iodobenzene molecule effectively blocks cis attack by chloride ion at carbons 1 and 3.

The steric requirements of the large anion (Ph–I–Cl$^-$) can also be used to explain the fact that Cristol et al.[11] obtained trans addition of chlorine in the reaction of acenaphthylene with iodobenzene dichloride. Tanner and Gidley[2] concluded that this reaction must be going by a radical mechanism since ionic addition of molecular chlorine to acenaphthylene gave only cis addition. However, the large anion from iodobenzene would probably prefer to add trans while the small chloride ion could add cis.

The increase in trans 1,4 addition and the decrease in cis 1,2 addition in the reaction between **1** and antimony pentachloride has also been rationalized on the basis of a large anion ($SbCl_4^-$ or $SbCl_6^-$) in the ion pair.[5]

The small amount of cis 1,2 addition (**1a, 2a**) which does occur in the reaction of **1** and **2** with iodobenzene dichloride is probably not the result of a concerted, molecular process (**5**, shown with diene **1**) since cis 1,2-dichloride formation with this chlorinating agent in the case of other olefins has been interpreted in other ways,[2] or simply has not been observed.[11,12] The cis 1,4-dichlorides (**1c** and **2c**) can not be formed by a concerted cis 1,4 addition since this suprafacial addition would be forbidden with iodobenzene dichloride as has been explained with antimony pentachloride.[13]



5

Experimental Section

Materials. Both iodobenzene dichloride[14] and trichloramine[15] were prepared as described in *Organic Syntheses*. Antimony pentachloride was obtained from Alfa Products.

Reaction Conditions. Reactions were carried out under nitrogen (unless oxygen was required as an inhibitor) and at the following temperatures: trichloramine and antimony pentachloride, −10 °C; and iodobenzene dichloride, room temperature. The dienes were dissolved in the appropriate amount of solvent to give a mole fraction of 0.02. The chlorinating agents were added to a stirred solution of the dienes in such amounts to consume 10 and 20% of the diene in dilute and neat solutions, respectively. The method of addition of the chlorinating agent depended on the reaction conditions: with dilute solutions, antimony pentachloride and iodobenzene dichloride were added as ca. 5% solution in the appropriate solvent; and in neat reactions, antimony pentachloride was added neat, and iodobenzene dichloride as a solid. Under all conditions trichloramine was added as a solution (0.6–0.7 M) in the appropriate solvent. The approximate volumes of dilute reaction mixtures are (ml): CH_2Cl_2, 22; CCl_4, 32; and C_5H_{12}, 38.

Identification and Analysis of Products. The cyclopentadiene dichlorides have already been reported,[3] and the procedures for establishing the structures of the cyclohexadiene dichlorides are described elsewhere.[4] The dichlorides from both dienes were analyzed by VPC under the following conditions: (cyclopentadiene), 7 ft × 0.125 in. column (SS) at 62 °C packed with β,β-oxydipropionitrile (2.5%) on 80–100 mesh Chromosorb W (AWDMCS) with retention times (min) of 4.4, 7.4, 20.6, and 22.6 for **1b, 1d, 1c,** and **1a,** respectively; and (cyclohexadiene),[16] 6 ft × 0.125 in. column (SS) at 57 °C packed with SE-30 (2.5%) on 80–100 mesh Chromosorb W (AWDMCS) with retention times (min) of 5.8, 7.2, 7.9, and 9.2 for **2b, 2d, 2c,** and **2a,** respectively. The stability of the dichlorides under these reaction and analysis conditions have been discussed elsewhere.[3-5]

Acknowledgment. Support for this work was provided by the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Atlantic Richfield Foundation.

Registry No.—**1a,** 51502-28-4; **1b,** 31572-43-7; **1c,** 31572-45-9; **1d,** 31572-44-8; **2a,** 53921-00-9; **2b,** 53920-98-2; **2c,** 54112-34-4; **2d,** 53920-99-3; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; iodobenzene dichloride, 932-72-9; trichloroamine, 10025-85-1.

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(1) K. W. Field and P. Kovacic, *J. Org. Chem.*, **36,** 3566 (1971).
(2) D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, **33,** 38 (1968).
(3) V. L. Heasley, G. E. Heasley, P. D. Davis, D. M. Ingle, and K. D. Rold, *J. Org. Chem.*, **39,** 736 (1974).
(4) G. E. Heasley, V. L. Heasley, D. Strickland, G. McClung, D. M. Ingle, P. D. Davis, T. S. Ungermann, K. D. Rold, and D. Hayse, *J. Org. Chem.*, in press.
(5) The mechanisms of the reactions of antimony pentachloride with olefins and dienes (including cyclopentadiene) is discussed in the following article: V. L. Heasley, G. E. Heasley, K. D. Rold, D. Titterington, C. Leach, D. McKee, and B. Gipe, unpublished work. A study on the reaction of butadiene with antimony pentachloride has recently been reported.[13]
(6) Molecular oxygen also had no effect on the product ratios. Field and Kovacic (ref 1) observed that solvents had no effect on the meso/*dl* ratio in the reaction between *cis*-2-butene and trichloramine, and that inhibitors did not affect the reactions with cyclohexene.
(7) We observed in a separate study that radical addition of methyl hypochlorite to isoprene resulted primarily in 1,4 addition ($CH_3OC–C–C{=}C–C–Cl$) although the main contributor to the intermediate resonance system must be the tertiary radical ($CH_3OC–C–C–C{=}C$). Apparently steric preference is involved in the attack of the radical on methyl hypochlorite.
(8) Although this chlorination was done under radical conditions, we feel that the addition may be occurring primarily by an ionic mechanism since the product ratios are so similar to the ionic reactions. Under the conditions of entry 4 cyclohexane was chlorinated to give chlorocyclohexane confirming a radical component to the reaction, but it may be a minor one. At least there is no major change in product composition in going from radical to ionic conditions as was observed by Poutsma in the chlorination of butadiene [M. L. Poutsma, *J. Org. Chem.*, **31,** 4167 (1966)].
(9) Tanner and Gidley[2] found that in their reactions with iodobenzene dichloride *sym*-tr-*tert*-butylphenol was ineffective as a radical inhibitor. In our case 2,6-dimethyl-4-*tert*-butylphenol was much more effective at retarding rate and altering product composition than oxygen. However, the concentration of the phenol that we used was approximately 300 times greater than was used by Tanner and Gidley.
(10) Our evidence for the ionic addition of the chlorines from iodobenzene dichlorides to **1** and **2** under the conditions described in entries 5, 6, and 7 is as follows. (a) There is a significant change in product ratios between ionic conditions (entries 5, 6, and 7) and radical conditions (8 and 9) with an increase in trans 1,2 addition (**1b** and **2b**) under radical conditions which correlates with the radical addition of trichloramine. (b) The inhibitor, 2,6-dimethyl-4-*tert*-butylphenol, greatly retarded the rate of reaction of iodobenzene dichloride. Under radical conditions the reaction is complete in a few minutes whereas with the inhibitor a couple of days is required for complete reaction. (c) In a separate study butadiene reacted with iodobenzene dichloride in the presence of the inhibitor to give the ratio of dichlorides expected from ionic addition, and in the absence of the inhibitor (and in the presence of N_2 and ultraviolet illumination) the ratio of dichlorides indicated radical addition. [For a discussion of the ratio of dihalides expected from ionic and radical additions to butadiene see the studies on the chlorination[8] and bromination [V. L. Heasley and S. K. Taylor, *J. Org. Chem.*, **34,** 2779 (1969)] of this diene.] Further evidence confirming the ionic addition of iodobenzene dichloride in the presence of the inhibitor came from a comparison of the rates of addition to butadiene and cyclopentadiene (**1**). The latter was found to be immensely faster; this appears reasonable on the basis of the relative stabilities of the allylic cation (chloronium ion) intermediates.
(11) S. J. Cristol, F. R. Stermitz, and P. S. Ramsey, *J. Am. Chem. Soc.*, **78,** 4939 (1956).
(12) J. G. Traynham and D. B. Stone, Jr., *J. Org. Chem.*, 35, 2025 (1970).
(13) R. P. Vignes and J. Hamer, *J. Org. Chem.*, **39,** 849 (1974).
(14) H. J. Lucas and E. R. Kennedy, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 482.
(15) P. Kovacic and S. S. Chudhary, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 35.
(16) During the course of the present study it was determined that dichlorides **2a–d** could be separated under simpler conditions (a shorter column) than was reported in an earlier study.[4]

A Convenient Synthesis of 2,3,12,13-Tetrathia[4.4]metacyclophanes and 2,3,12,13-Tetrathia[4.4]paracyclophanes

Tim-Fat Tam, Po-Cheong Wong, Tak-Wai Siu, and Tze-Lock Chan*

Chemistry Department, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong

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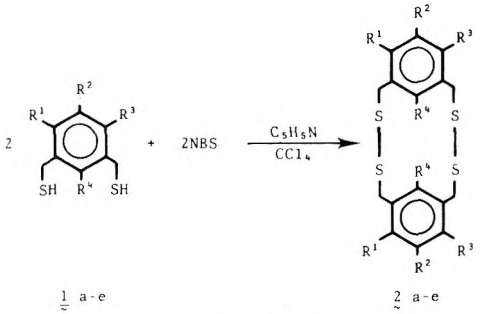
The potential of tetrathia[4.4]cyclophanes as useful synthetic precursors of bridged aromatic ring systems has been

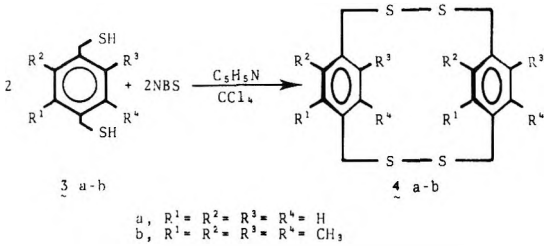
Table I. Preparation of 2 and 4 by Oxidation of 1 and 3 with NBS–Pyridine in CCl_4

Compd	Reaction time, h (temp, °C)	Mp, °C (recrystn solvent)	Yield,[a] %	Molecular formula[b]	Method of isolation[c]
2a	10 (40)	170–171[d] (ethanol)	56		A
2b	12 (50)	209–210 (hexane)	60	$C_{18}H_{20}S_4$	A
2c	15 (40)	252–254 (acetone)	72	$C_{20}H_{24}S_4$	A
2d	18 (76)	283–285 (benzene)	62	$C_{22}H_{28}S_4$	A
2e	16 (25)	265–267 dec (benzene)	22	$C_{22}H_{28}S_4$	B
4a	20 (25)	250–252 dec (benzene)	8	$C_{16}H_{16}S_4$	B
4b	18 (76)	286–288 (CCl_4)	15	$C_{24}H_{32}S_4$	B

[a] Yields are for isolated and purified products. [b] Confirmed by mass spectral data, and satisfactory analytical values (±0.3% for C, H, and S) were reported for all new compounds listed in the table. [c] A, by direct crystallization; B, by chromatography over silica gel using benzene–petroleum ether (bp 50–75 °C) (1:4 or 1:5) followed by recrystallization from the solvent specified. [d] Lit.[1] mp 171.5–172.5 °C.

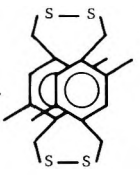
realized by the conversion of 2,3,12,13-tetrathia[4.4]metacyclophane (**2a**) and its 10,20-dimethyl derivative (**2**, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$) into the corresponding 2,11-dithia[3.3]metacyclophanes[1] which were the key intermediates for a series of interesting hydrocarbons including 15,16-dihydropyrenes.[2] In principle, this type of medium-size cyclic bisdisulfide can be prepared directly by oxidative coupling of appropriate *m*- and *p*-xylylene dimercaptans, but a general procedure is lacking in the literature. We report here a convenient method which not only provides reasonably good yields of symmetrical tetrathia[4.4]metacyclophanes **2**, thus complementing the two-step synthesis reported by Boekelheide and Mondt,[1] but also permits the preparation of 2,3,12,13-tetra[4.4]paracyclophanes (**4**) for the first time.





The procedure involves treatment of xylylene dimercaptans 1 or 3 with the appropriate molar quantity of *N*-bromosuccinimide (NBS) in carbon tetrachloride containing slight excess of pyridine. Isolation of products is effected by direct crystallization or column chromatography.

Seven successful cyclizations (Table I) were observed from nine xylylene dimercaptans examined in the present investigation. The lower yields for the formation of tetrathia[4.4]paracyclophanes 4 are readily accountable by their increased ring size. The only instance where the desired cyclization failed was with 4,6-bis(mercaptomethyl)isodurene (**1**, $R^1 = R^2 = R^3 = R^4 = CH_3$), which gave only polymeric products. In addition, 2,5-bis(mercaptomethyl)-*p*-xylene (**3**, $R^1 = R^3 = H$; $R^2 = R^4 = CH_3$) gave a coupling product with mp 249–251 °C and parent mass peak at *m/e* 392 whose structure can either be the syn (**5a**) or anti (**5b**) isomer. Inspection of molecular models reveals that these two isomers are not interconvertible by ring flipping. Unfortunately, its NMR spectrum ($CDCl_3$), which displayed singlets at δ 2.34 (3 H), 3.64 (2 H), and 6.82 (1 H), cannot distinguish between these two possibilities.



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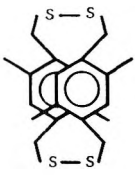

5 b

The facile oxidative coupling observed with NBS is remarkable since our earlier attempts to prepare **2** and **4** by employing other oxidants such as hydrogen peroxide, iodine, ferric chloride, and atmospheric oxygen under various conditions failed in almost all cases. Either polymerization occurred in such serious extents that product isolation was precluded or starting materials were recovered unchanged. The only exception was **1c**, which was cyclized into **2c** in 80% yield by air oxidation in ethanol containing excess sodium ethoxide.

Experimental Section[3]

Preparation of Dimercaptans 1 and 3. Compounds **1c–e** and **3b** were prepared by standard procedure[4] from the corresponding xylylene dichlorides which were in turn obtained by bischloromethylation of appropriately substituted methylbenzenes.[5] Compounds **1a, b** and **3a** were prepared similarly from the corresponding dibromides. All dimercaptans exhibited NMR spectra consistent with the assigned structures.

General Procedure for the Preparation of [4.4]cyclophanes 2 and 4. An equal molar mixture of 1 or 3 and NBS in a large volume of dry carbon tetrachloride (distilled over P_2O_5) containing a slight excess of pyridine was stirred at the temperature and for the durations specified in Table I. Removal of succinimide and pyridine hydrobromide from the reaction mixture was effected by extraction or washing with water. Product isolation from the residue was carried out by crystallization or column chromatography. Representative preparations are illustrated below.

6,7,8,16,17,18-Hexamethyl-2,3,12,13-tetrathia[4.4]metacyclophane (2d). To a solution of **1d** (1.70 g, 8 mmol) in 350 ml of dry carbon tetrachloride containing pyridine (2.0 g, excess) was added NBS (1.41 g, 8 mmol) in one portion and the mixture was stirred under reflux for 18 h. The reaction mixture was filtered hot and the cooled filtrate was extracted with water and dried over anhydrous $MgSO_4$. Removal of solvent in vacuo gave a fluffy white solid which was recrystallized from benzene to afford 1.05 g (62%) of pure **2d** as white, fluffy needles: mp 283–285 °C; NMR (CS_2) δ 6.45 (s, 1 H), 3.70 (s, 4 H), 2.21 (s, partially overlapped, ca. 6 H), and 2.11 (s, partially overlapped, ca. 3 H); mass spectrum (70 eV) *m/e* 420 (M^+).

2,3,12,13-Tetrathia[4.4]paracyclophane (4a). To a solution of **3a** (1.70 g, 10 mmol) in 400 ml of dry carbon tetrachloride containing pyridine (2.2 g, excess) was added NBS (1.78 g, 10 mmol) in

one portion, and the mixture was stirred at room temperature for 20 h during which period a white solid gradually formed. The resulting mixture was carefully evaporated to dryness under reduced pressure and the residue was successively washed with water and methanol followed by repeated extraction with warm chloroform. The dried (anhydrous $MgSO_4$) chloroform solution was concentrated to ca. 10 ml and poured into a column of silica gel. The fractions eluted by benzene–petroleum ether (bp 50–75 °C) (1:4) on evaporation left a white solid which was recrystallized from benzene to give 130 mg (8%) of pure **4a**: mp 250–252 °C dec; NMR ($CDCl_3$) δ 6.84 (s, 1 H), 3.62 (s, 1 H); mass spectrum (70 eV) *m/e* 336 (M^+).

Acknowledgment. We are grateful to Mr. K. W. Ho for providing mass spectral data.

Registry No.—**1a**, 41563-69-3; **1b**, 42082-63-3; **1c**, 58074-29-6; **1d**, 58074-30-9; **1e**, 10074-13-2; **2a**, 27929-85-7; **2b**, 58074-31-0; **2c**, 58074-32-1; **2d**, 58074-33-2; **2e**, 58074-34-3; **3a**, 105-09-9; **3b**, 10519-84-3; **4a**, 58074-35-4; **4b**, 58074-36-5; NBS, 128-08-5.

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(3) All melting points were determined on a Koefler hot stage and are uncorrected. Nuclear magnetic resonance spectra were taken on a JEOL 60HL spectrometer using tetramethylsilane as internal standard. Mass spectral data were obtained on a Varian M66 instrument. Elemental analyses were performed by Australian Microanalytical Service, Melbourne.
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(5) R. C. Fuson and C. H. McKeever, *Org. React.*, **1**, 63 (1942).

Protic Acid Catalyzed Thiono–Thiolo Rearrangements of Phosphorus Esters

Wojciech J. Stec,* Bogdan Uznański, Karol Bruzik, and Jan Michalski*

Centre of Molecular and Macromolecular Studies, Polish Academy of Science, Department of Heteroorganic Compounds, 90-362 Łódź, Boczna 5, Poland

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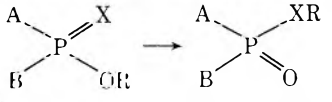
The thiono–thiolo rearrangement of organophosphorus thionoesters (eq 1) is known to be effected thermally as well as by alkyl halides, Lewis acids,[1] and electron impact.[2]

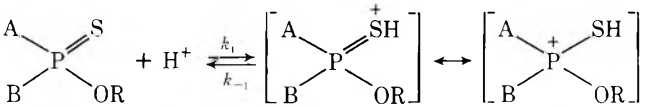


(1)

X = S, Se; R = primary alkyl

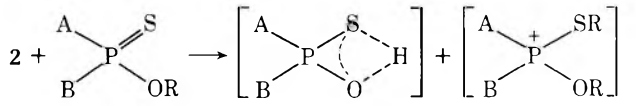
We have found that protic acids can also cause this type of rearrangement with the rate of reaction depending on the nature of the A, B, and R substituents and also on the strength of the acid used. The rearrangement can be monitored by means of either ^{31}P NMR[3] or by ^1H NMR.[4] The main limitation of our new procedure for thiono–thiolo rearrangements lies in its inapplicability to compounds with P–N bonds; such bonds are labile in acidic conditions.[5] Those esters when R is secondary or tertiary alkyl are also unsuitable reactants. The described method of rearrangement of phosphorothionates into isomeric phosphorothiolates under the influence of protic acids possesses one main advantage; it gives very clean and easily isolable products. Simple removal of trifluoroacetic acid by distillation and neutralization of the 1:1 complex[6] (>P=O·····$HOCOCF_3$) allows isolation of pure phosphorothiolate. For example, dissolving trimethyl phosphorothionate and trifluoro- or trichloroacetic acid (1:10 mol/mol) results in rearrangement to *O,O,S*-trimethyl phosphorothiolate. The half-life times $t_{1/2}$, measured at 55 °C, were 5.95 and 82.9 h, respectively. It has been also found that $t_{1/2}$ of conversion at 55 °C of trimethyl phosphorothionate, *O,O*-dimethyl phenylphosphonothionate, and *O*-methyl diphenylphosphonothionate diluted in trifluoroacetic acid (1:10 mol/mol) were respectively 0.46, 1.2, and 3.91 h.

Our preliminary observations allow us to draw some conclusions about the mechanism of the rearrangement. Intermolecular character has been demonstrated in the following experiment. The mixture of trimethyl and triethyl phosphorothionate (1:1) in trifluoroacetic acid solution gave the following products: $(MeO)_2P(O)SMe$, $(EtO)_2P(O)SEt$, $(MeO)_2P(O)SEt$, and $(EtO)_2P(O)SMe$. The last two compounds clearly indicate an intermolecular type of process. In addition $(EtO)_2P(O)SEt$ and $(MeO)_2P(O)SMe$, when stored in CF_3COOH solution under the same conditions, did not lead to detectable amounts of $(MeO)_2P(O)SEt$ or $(EtO)_2P(O)SMe$. It seems reasonable that the protonation of thiophosphoryl sulfur takes place in the first step of the reaction. The absorption band for the thiophosphoryl group, $\nu_{P=S}$ 635 cm^{-1} in $Ph_2P(S)OMe$ measured in CCl_4 solution (10%) shifts to 628 cm^{-1} when an equimolar amount of CF_3COOH is added, while the $\nu_{P=O}$ 1030 cm^{-1} of the bridging oxygen remains unchanged. Consequently, the formation of a quasi-phosphonium cation has to be considered:



1 2

Equilibrium between **1** and **2** depends on the pK_a of the acid and the nature of the substituents A, B, and R. Quasi-phosphonium cation **2** possesses strong alkylating properties[7] and a "soft" base in the reaction medium would be immediately alkylated. The sulfur atom of the thiophosphoryl group can be considered as a "soft" base, which, in the presence of **2** would be alkylated immediately with formation of another ion **4** and free acid **3**.



3 4

Cationic species **4** would also possess alkylating properties[7] and could alkylate another molecule of thionoester **1** or the free thio acid **3**, with liberation of rearranged thioloester–trifluoroacetic acid complex. The formation of 1:1 complexes of phosphoryl compounds with protic acids is known.[6] It has to be emphasized that in several experiments the presence of dialkyl hydrogen phosphorothioate **3** has not been detected. Also methyl trifluoroacetate is not formed in the reactions investigated. *O-n*-Propyl diphenylphosphinothionate rearranges in CF_3COOH solution to *S-n*-propyl derivative. No traces of *S*-isopropyl ester were found among the reaction products. Thus, carbocation R^+ is then presumably not responsible for the S-alkylation process.

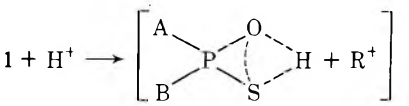


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Table I. Isomerization of Alkyl Phosphoro(phosphino)thionates into Corresponding Phosphoro(phosphino)thiolates Catalyzed by Protic Acids

No.	Substrate	Temp, °C	Acid	Molar ratio substrate: acid	Yield, %	Product, ^{31}P NMR, bp or mp	Registry no.
1	$(CH_3O)_3P{=}S$	10	H_2SO_4	1:1	98	$(CH_3O)_2P(O)SCH_3$[c]	152-20-5
2	$(CH_3O)_3P{=}S$	20	CF_3COOH	1:2	92	$(CH_3O)_2P(O)SCH_3$	
3	$(CH_3)_2P(S)OCH_2CH{=}CHC_6H_5$	20	CF_3COOH	1:1	71	$(CH_3)_2P(O)SCH_2CH{=}CHC_6H_5$ $\delta_{^{31}P}$ −47.6 ppm (H_3PO_4) mp 73 °C (petroleum ether)	57969-75-2
4	$(CH_3)_2P(S)OCH_2CH{=}CD_2$	20	CF_3COOH	1:3	60	$(CH_3)_2P(O)SCH_2CH{=}CD_2$ bp 70 °C (0.001 mm) $\delta_{^{31}P}$ −51.5 ppm (H_3PO_4)	57969-76-3
5	$(CH_3O)_2P(S)OC{=}CHCl$ $2,5\text{-}C_6H_3Cl_2$	70	CF_3COOH	1:4	83	$CH_3OP(O)(SCH_3)OC{=}CHCl$ $2,5\text{-}C_6H_3Cl_2$ $\delta_{^{31}P}$ −27.5 ppm (H_3PO_4) mp 58–59 °C	57969-77-4
6	*trans*-$OCH_2CH_2CH(CH_3)OP(S)OCH_3$[a]	20	CF_3COOH	1:3	81	*cis*-$OCH_2CH_2CH(CH_3)OP(O)SCH_3$[d] $\delta_{^{31}P}$ −22.8 ppm (H_3PO_4) bp 110–115 °C (0.2 mm)	50902-83-5
7	*cis*-$OCH_2CH_2CH(CH_3)OP(S)OCH_3$[a]	20	CF_3COOH	1:3	82	*trans*-$OCH_2CH_2CH(CH_3)OP(O)SCH_3$[d] $\delta_{^{31}P}$ −14.0 ppm (H_3PO_4) bp 105–110 °C (0.1 mm)	50902-84-6
8	*trans*-$OCH_2CH_2CH(CH_3)OP(Se)OCH_3$[b]	20	CF_3COOH	1:3	80	*cis*-$OCH_2CH_2CH(CH_3)OP(O)SeCH_3$[b] $\delta_{^{31}P}$ −18.1 ppm (H_3PO_4) mp 77–77.5 °C (ether–acetone)	39826-74-9
9	*cis*-$OCH_2CH_2CH(CH_3)OP(Se)OCH_3$[b]	20	CF_3COOH	1:3	86	*trans*-$OCH_2CH_2CH(CH_3)OP(O)SeCH_3$[b] $\delta_{^{31}P}$ −10.8 ppm (H_3PO_4) mp 58–58.5 °C (ether–acetone)	39826-71-6

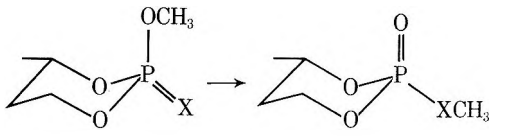
[a] C. L. Bodkin and O. Simpson, *J. Chem. Soc. B*, 1136 (1971). [b] M. Mikolajczyk and J. Luczak, *Tetrahedron*, **28**, 5411 (1972). [c] G. Hilgetag and H. Teichmann, *J. Prakt. Chem.*, **8**, 121 (1959). [d] B. Ziemnicka, *Zesz. Nauk. Politech. Lodz. Chem.*, **27**, 170 (1973); *Chem. Abstr.*, **80**, 107892 (1974).

In the light of the above overall explanation it is clear that secondary alkyl esters do not undergo this rearrangement because secondary and tertiary carbon atoms of R in **2** and/or **4** are less available for nucleophilic attack on the sulfur atom. Experimental results are collected in Table I.

Some experiments require further comments.

(a) Phosphoroselenoates (expt 7 and 8) undergo more facile rearrangement than their sulfur analogues owing to more enhanced nucleophilicity of the "soft" selenium atom.

(b) Fifty percent conversion of *cis*-2-methoxy-2-thiono-4-methyl-1,3,2-dioxaphosphorinane to *trans*-2-methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (expt 6) is achieved three times faster than that of *trans*- into *cis*- (expt 5). The faster rearrangement of the isomer with an axial sulfur atom may be explained in terms of an enhanced Lewis basicity of axially orientated sulfur relative to one in an equatorial position. This conclusion as applied to axial and equatorial oxygen has been reached by Verkade.[8]



trans, X = S, Se cis

(c) Rearrangement of *O*-allyl dimethylphosphinothionates proceeds much faster than that of other *O*-alkyl derivatives. However, rearrangement of *O*-γ-phenylallyl dimethylphosphinothioate (expt 3) gives exclusively *S*-γ-phenylallyl ester, without any trace of the *S*-α-phenyl isomer. The same product was obtained by thermal rearrangement of $Me_2P(S)OCH_2CH{=}CHC_6H_5$. Its structure was proved by ^1H NMR spectra: δ_{PSCH_2} −3.8 ppm, $^3J_{PSCH_2}$ = 12.3 Hz (2 H). The rearrangement of *O*-allyl-*3,3-d*$_2$ dimethylphosphinothionate (δ_{POCH_2} −4.56 ppm, $^3J_{POCH_2}$ = 10.9 Hz) gave *S*-allyl-*3,3-d*$_2$ dimethylphosphinothiolate [δ_{PSCH_2} −3.56 ppm, $^3J_{PSCH_2}$ = 11.9 Hz (2 H), Me_4Si internal standard]. These findings argue against a cyclic Claisen-type mechanism of rearrangement, postulated by Pudovik and Aladsheva[9] on the basis of their studies on the rearrangements of *O*-crotyl *O,O*-dimethylphosphorothionate. Enhanced reactivity of allyl esters may be explained in terms of known higher electrophilic reactivity of the allyl group toward nucleophiles.

Experimental Section

All melting and boiling points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use. ^1H NMR spectra were recorded at 60 MHz with a JEOL C-60H spectrometer and Perkin-Elmer R12B. ^{31}P NMR spectra were obtained on a JEOL C-60H operating at 24.3 MHz with external H_3PO_4 as the reference. Mass spectra were obtained on an LKB-9000S spectrometer at 70 eV ionizing energy. GLC analyses were performed on a Varian Aerograph 1520. Ir spectra were obtained on a Zeiss-Jena UR-10.

General Procedure. At the temperature given in Table I the thionoester was added to the protic acid with intensive stirring and external cooling. Reactions were followed by means of ^1H and ^{31}P NMR. When the conversion of the substrate to the product reached 95%, excess of trifluoroacetic acid was removed under reduced pressure, the residue was diluted with either benzene or ether, and aqueous sodium carbonate was added for neutralization of the molar amount of acid involved in complex formation.[6] When H_2SO_4 was used, neutralization was done with gaseous ammonia. Following dilution by ether, ammonium sulfate was collected by filtration. The organic layer was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure, and the product was distilled or crystallized from a suitable solvent. Satisfactory analyses were obtained for all reported compounds.

***O*-γ-Phenylallyl dimethylphosphinothionate** was obtained by reaction of cinnamyl alcohol with an equimolar amount of dimethyl phosphinobromothioate[10] in the presence of triethylamine. Attempts at its distillation caused rearrangement of the syrupy liquid to the thiolo isomer: ^{31}P NMR δ −91.3 ppm (external H_3PO_4); ^1H NMR δ_{POCH_2} −4.7 ppm, $^3J_{POCH_2}$ = 11.4 Hz.

***O*-Allyl-*3,3-d*$_2$ dimethylphosphinothionate** was prepared by condensation of allyl-*3,3-d*$_2$ alcohol[11] with dimethyl phosphinobromothioate in the presence of triethylamine. Distilled product, bp 35–40 °C (0.05 mmHg), was checked by ^{31}P NMR ($\delta_{^{31}P}$ −93 ppm, external H_3PO_4) and GC–MS.

Registry No.—**1**, 152-18-1; **3**, 57969-73-0; **4**, 57969-74-1; **5**, 1217-91-0; **6**, 23168-88-9; **7**, 23168-89-0; **8**, 33996-02-0; **9**, 33996-01-9; cinnamyl alcohol, 104-54-1; dimethyl phosphinobromothioate, 6839-93-6; allyl-*3,3-d*$_2$ alcohol, 16315-95-0.

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The Position of the Phenolic Function in Tiliacorine and Related Alkaloids[1]

Maurice Shamma* and James E. Foy

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Tuticorin R. Govindachari and Narayana Viswanathan

CIBA-GEIGY Research Centre, Goregaon East, Bombay, India

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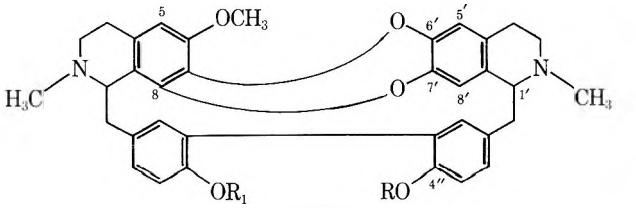
The bisbenzylisoquinoline alkaloid tiliacorine, found in *Tiliacora racemosa* Colebr. [*T. acuminata* (Lam.) Miers], has been assigned structure **1a** or **1b** since the exact position of the phenol in the lower half of the alkaloid was still uncertain.[2] We now wish to present evidence in favor of expression **1a** for tiliacorine.



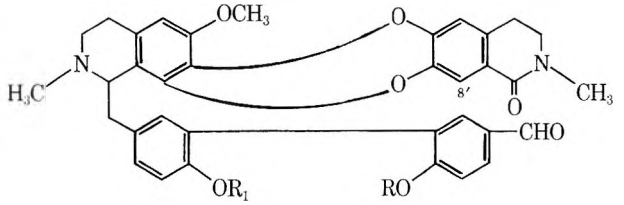
1a, R = H; R_1 = CH_3
b, R = CH_3; R_1 = H
c, R = R_1 = CH_3
d, R = Ac; R_1 = CH_3

Our attention was called to this problem during a study of the selective oxidation of several bisbenzylisoquinolines using potassium permanganate in acetone. That investigation revealed that in every case oxidation occurred at the doubly benzylic bond of the isoquinoline moiety unsubstituted at C-8′ (or C-8) to afford an aldehydo lactam.[3]

Treatment of the known *O*-methyltiliacorine (**1c**)[2] with excess potassium permanganate in refluxing acetone fol-

lowed by preparative TLC gave an 8% yield of the desired aldehydo lactam oxidation product **2c**, ν_{max} ($CHCl_3$) 1630 (lactam) and 1705 cm^{-1} (aromatic aldehyde). Close inspection of the NMR spectrum revealed that the C-8′ proton appeared downfield at δ 7.20, consistent with an aromatic hydrogen peri to a lactam carbonyl.[3] Thus, oxidation had taken place, as expected, at the doubly benzylic bond of the isoquinoline unit unsubstituted at C-8′.

The oxidation of tiliacorine acetate (**1d**) was then performed under identical conditions. Basic hydrolysis of the O-acetylated oxidation product **2b** yielded the phenolic aldehydo lactam **2a** whose uv spectrum, λ_{max} (EtOH) 212,



2a, R = H; $R_1 = CH_3$
b, R = Ac; $R_1 = CH_3$
c, R = $R_1 = CH_3$

282, and 310 sh nm (log ϵ 4.10, 3.44 and 2.94), showed a strong bathochromic shift in base to λ_{max} ($EtOH-OH^-$) 230, 292, and 340 nm (log ϵ 4.00, 3.27, and 3.21). A bathochromic shift of this magnitude is indicative of a phenolic function para to an aromatic aldehyde,[4] so that tiliacorine must be represented by expression **1a**.

It has already been shown that tiliacorine and tiliacorinine are diastereomeric, so that the latter is also represented by **1a**.[5] Nortiliacorinine A and nortiliacorinine B are *N*-nor bases belonging to the tiliacorinine series.[5] Therefore, the present study also settles the position of the phenolic functions of these alkaloids which must be located at C-4″. The absolute configuration of tiliacorine and its analogues still remains to be established.

It should be noted in conclusion that the two lower rings of tiliacorine type alkaloids are linked through a direct carbon to carbon bond, rather than through the much more common diaryl ether bridge.[6] This unusual structural feature precludes facile chemical interrelationship between tiliacorine bases and other bisbenzylisoquinolines of established structure and stereochemistry.[8]

Experimental Section

NMR spectra were obtained on a Varian A-60A with $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were run on an MS-901 spectrometer. All TLC (thin layer chromatography) was on Merck EM F-254 silica gel plates.

General Oxidation Procedure. The bisbenzylisoquinoline, in the present case *O*-methyltiliacorine (**1c**),[2,5] 250 mg, was dissolved in 250 ml of acetone and heated to reflux. Solid $KMnO_4$ (250 mg) was added all at once, and the mixture boiled for an additional 1 h. Filtration of the MnO_2 followed by evaporation of the solvent yielded a gum which was subjected to TLC (10% MeOH–90% $CHCl_3$). Collection of the highest R_f alkaloidal band, detected by short-wave uv light or by the iodoplatinate spray reagent,[7] gave 21 mg (8%) of **2c**, colorless crystals: mp 174–175 °C ($MeOH-C_6H_6$); λ_{max} (EtOH) 212, 282, and 310 sh nm (log ϵ 4.05, 3.31, and 2.90). The more prominent features of the NMR spectrum were at δ 2.65 (3 H, s, NCH_3), 3.09 (3 H, s, lactam NCH_3), 3.70 (3 H, s. OCH_3), 3.81 (6 H, s, 2 OCH_3), 6.27 (1 H, s, C-5), 7.20 (1 H, s, 8′-H), and 9.80 (1 H, s, –CHO). The mass spectrum showed *m/e* 620 (M^+, $C_{37}H_{36}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), and 255 ($C_{16}H_{15}O_3$); high resolution M^+ calcd 620.2520, found 620.2466.

The oxidation of tiliacorine acetate (**1d**)[5] was carried out under conditions essentially identical with those described above. The yield of aldehydo lactam **2b** was 8%: ν_{max} ($CHCl_3$) 1630 (lactam), 1705 (aromatic aldehyde), and 1765 cm^{-1} (acetate); λ_{max} (EtOH) 212, 270, and 320 sh nm (log ϵ 4.01, 3.44, and 2.86). The mass spectrum showed peaks at *m/e* 648 (M^+, $C_{38}H_{36}N_2O_8$), 605 ($C_{36}H_{33}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), 283 ($C_{17}H_{15}O_4$), and 240 ($C_{15}H_{12}O_3$); high resolution M^+ calcd 648.2770, found 648.2703.

Hydrolysis of 2b. The acetate **2b** (20 mg) was added to 10 ml of a solution of MeOH previously saturated with K_2CO_3. The mixture was stirred at room temperature for 2 h. Work-up provided 18 mg (90%) of **2a**: mp 185–187 °C (MeOH); ν_{max} ($CHCl_3$) 1630 and 1705 cm^{-1}. The NMR spectrum shows peaks at δ 2.35 (3 H, s, NCH_3), 3.08 (3 H, s, lactam NCH_3), 3.80 (9 H, s, 3 OCH_3), 6.28, 6.64, 6.90, 7.17, 7.67, and 7.85 (6 H, each as s, 6 aromatic H), and 9.86 (1 H, s, –CHO). The mass spectrum had peaks at *m/e* 606 (M^+, $C_{36}H_{34}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), and 241 ($C_{15}H_{13}O_3$); high resolution M^+ calcd 606.2364, found 606.2295.

Registry No.—**1a**, 27073-72-9; **1c**, 23944-12-9; **1d**, 58220-09-0; **2a**, 58220-10-3; **2b**, 58220-11-4; **2c**, 58220-12-5.

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(8) **Note Added In Proof.** A similar conclusion regarding the position of the phenolic function in tiliacorine was reached independently by Professor Norman S. Bhacca of Louisiana State University.

Facile Intramolecular Displacement of Fluoride in Reaction of γ-Fluorobutyronitrile with Phenylmagnesium Bromide

Allen E. Kemppainen, Michael J. Thomas, and Peter J. Wagner*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

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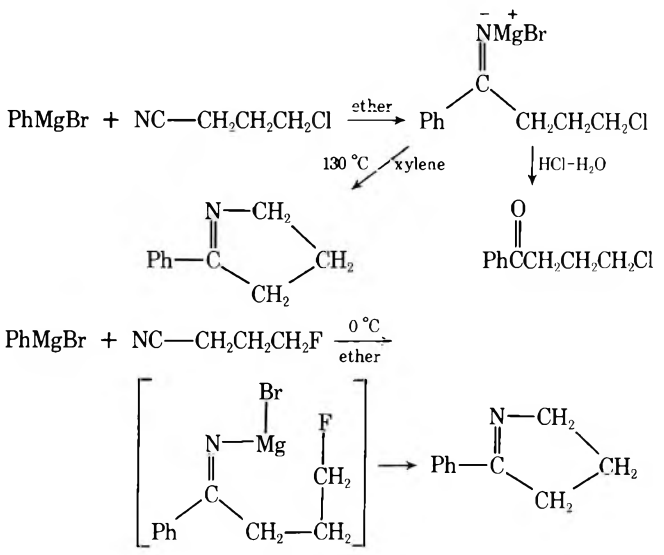
2-Aryl-1-pyrrolines (5-aryl-3,4-dihydro-2*H*-pyrroles) can be readily synthesized by the addition of aryl Grignard reagents to γ-chloro- or -bromobutyronitrile.[1-4] When cyclization is desired, the magnesium bromide salt of the imine or the free imine is heated. If the ethereal solution of the imine salt is worked up as usual, by acidification and hydrolysis,[5] the γ-halo ketones are obtained in good yields.[1,6] We find that when phenyl Grignard reagent is added to γ-fluorobutyronitrile, the pyrroline is formed even without replacement of solvent and heating.

An ether solution of phenylmagnesium bromide was prepared as usual. Addition of γ-fluoronitrile to this solution produced a more exothermic reaction than normal for aliphatic nitriles. In one run the solution was allowed to reflux during the addition; in another it was kept in an ice bath. The reaction solution was worked up so as to hydrolyze any γ-fluoroimine to the ketone. The only product obtained was identified as 2-phenyl-1-pyrroline.

The very exothermic nature of the Grignard–fluoronitrile reaction and the lack of ketone product suggest that the imine anion readily displaces the fluoride under the mild conditions of the Grignard-to-nitrile addition. Since the chloro- and bromoimine salts do not undergo internal displacement except at high temperature, and since normally Br > Cl ≫ F as leaving groups, we must postulate that the magnesium ion assists the displacement by bonding specifically to the fluorine. The unusual nature of the Grignard reaction is emphasized by the selective displace-



ment of chloride by sodium cyanide from 1-chloro-3-fluoropropane which we used in one preparation of the fluoronitrile.

We have not investigated whether magnesium salts in general easily displace fluoride from alkyl fluorides.

Preparation of 2-Phenyl-1-pyrroline. Phenylmagnesium bromide (0.33 mol) was prepared as usual by slow addition of 53 g of bromobenzene in an equal volume of anhydrous ether to 8 g of magnesium turnings in a round-bottomed flask fitted with a reflux condenser and magnetic stirrer. The solution was then cooled in an ice bath while 21 g (0.24 mol) of γ-fluorobutyronitrile was added dropwise. The addition caused vigorous refluxing of the solution and precipitation of a flaky white substance. After the addition was complete, the entire mixture was poured into a 500-ml beaker half filled with ice and 50 ml of concentrated HCl and was stirred until all solids were dissolved. The cold aqueous layer was washed with ether and placed on a steam bath for 1 h. Extraction of the cooled solution with ether yielded only a trace of an oily substance. Solid sodium carbonate was added to the aqueous solution until it was slightly basic. Warming the solution on a steam bath caused a reddish oil to separate. Extraction with ether yielded 20 ml of a product which was vacuum distilled on a micro-Vigreux column. A slightly cloudy, colorless liquid (13 g) was collected at 102–104 °C (5 Torr). The product was purified by being passed through a small quantity of alumina and then being recrystallized from hexane immersed in dry ice. The resulting clear liquid produced only one peak in VPC analysis: ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 2 H, ortho H), 7.42 (m, 3H, meta and para H), 4.09 (t, J = 8.0 Hz, 2 H, $-CH_2N=$), 2.95 (t, J = 8.0 Hz, 2 H, $CH_2C=N$), 2.00 (quintet, J = 8 Hz, 2 H, $C-CH_2C$); ir (CCl_4) 3030, 2960, 2855, 1610, 1570, 1490, 1440, 1335, 1305, 1035, 1020, 985, 960, 685 cm^{-1}; MS (15 eV) *m/e* (rel intensity) 145 (100), 144 (24), 117 (94), 105, 104, 91, 77, 68.

Anal. Calcd for $C_{10}H_{11}N$: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.83; H, 7.66; N, 9.58.

This procedure was repeated 5 years later by another worker, with identical results. The addition of nitrile to Grignard was done at 0 °C; the acidified solution was not heated.

Preparation of γ-Fluorobutyronitrile. A. Ethylene glycol (250 ml) and 200 ml of toluene were placed in a flask equipped with a Dean-Stark trap, reflux condenser, and drying tube. $KF{\cdot}2H_2O$ (282 g, 3 mol) was added in three portions, with 2–3 h refluxing between additions. In the first 10 h of refluxing, 108 ml of water was removed. Further refluxing overnight removed traces of water. Toluene (150 ml) was then distilled off. To the cooled solution 315 g of 1-bromo-3-chloropropane (Michigan Chemical Co.) was added over 15 min. The mixture was then heated to 100 °C and was stirred vigorously for 8 h. A distillation head was then substituted for the reflux condenser and everything boiling between 70 and 100 °C was collected and dried over calcium chloride. Redistillation yielded 53 g (0.5 mol) of crude 1-chloro-3-fluoropropane (probably containing some of the 3-bromo compound), bp 75–90 °C. This 1-chloro-3-fluoropropane (53 g) was added dropwise to a stirred solution of 50 g of NaCN in 75 ml of Me_2SO. The Me_2SO solution had been preheated to 60 °C and maintained a temperature range of 75–95 °C during addition. The mixture was stirred for 5 h after addition was complete. It was then added to 500 ml of of water and extracted with ether.

The ether layer was washed with 1 N HCl, dried over $CaCl_2$, and distilled. γ-Fluorobutyronitrile (21.5 g, 0.24 mol) was collected as a clear, colorless liquid: bp 162–166 °C; NMR (60 MHz, neat) δ 4.83, 4.05 (2 H, each a t, J = 5 Hz, FCH_2, J_{H-F} = 47 Hz), 2.45 (t, 2 H, J = 6 Hz, CH_2CN), 2.56–1.50 (2 H, complex, roughly a doublet of quintets, middle CH_2, $J_{F-H} \simeq$ 32 Hz); ir (film) 2980, 2910, 2250, 1475, 1430, 1390, 1035, 925, 895 cm^{-1}.

B. $KF{\cdot}2H_2O$ (283 g, 3 mol) was heated under vacuum in a 1-l. flask to drive off most of the water. Glycerine (300 g) was added to the cooled salt. The solution was stirred and warmed to 50 °C, whereupon 126 g of γ-chlorobutyronitrile (Eastman Technical) was added and the pot temperature was gradually increased to 200 °C. A product distilled over between 140 and 160 °C. This distillate was added to 60 ml of chloroform and the organic layer was dried over $MgSO_4$. Distillation provided 42 g (47% yield) of the fluoronitrile, ≥95% pure to VPC analysis.

Registry No.—$KF{\cdot}2H_2O$, 13455-21-5; NaCN, 143-33-9; 2-phenyl-1-pyrroline, 700-91-4; bromobenzene, 108-86-1; γ-fluorobutyronitrile, 407-83-0; 1-bromo-3-chloropropane, 109-70-6; 1-chloro-3-fluoropropane, 462-38-4; γ-chlorobutyronitrile, 628-20-6.

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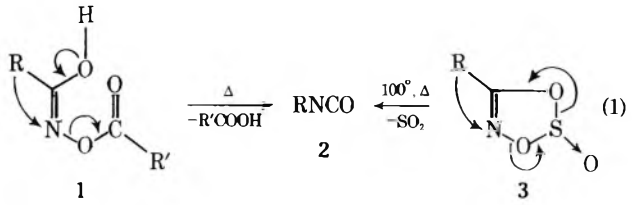
Thermolysis of 1,3,2,4-Dioxathiazole 2-Oxides. Nitrile Oxide Intermediates

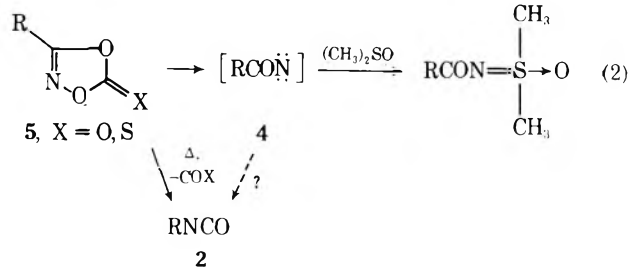
Summary. Nitrile oxide intermediates were trapped during the thermolysis of 5-substituted 1,3,2,4-dioxathiazole 2-oxides using dimethyl acetylenedicarboxylate, ethyl propiolate, and norbornene as dipolarophiles.

Sir: The thermal rearrangement of hydroxamic acid esters **1** to isocyanates **2** (Lossen rearrangement)[1,2] has been studied for many years and is currently considered to be a concerted process similar to the Hoffman and Curtius rearrangements.[3] The cyclic sulfite esters **3** also yield isocyanates in excellent yields[4-7] and have been postulated[7] to decompose by a similar (concerted) mechanism (eq 1).



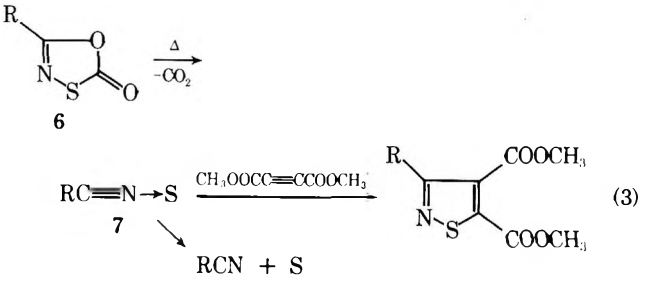
(1)

Attempts to trap intermediates during the course of this type of decomposition have been uniformly unsuccessful. Acyl nitrenes **4** were considered as potential intermediates by early investigators but precursors of this type are reported[3] to be formed only under photolytic conditions and not to rearrange readily to isocyanates. By contrast, however, the cyclic hydroxamate esters **5** also yield isocyanates in high yields on thermal decomposition[4,5] but in the presence of certain trapping agents (dimethyl sulfoxide,[6] triphenylarsine[8]) are reported to produce derivatives indicative of acyl nitrene intermediates (eq 2).



(2)

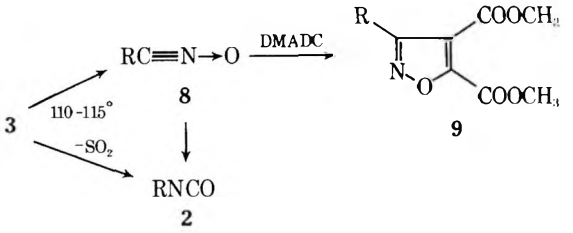
Similar attempts[6] to trap intermediates during decomposition of **3**, however, were not successful. Cyclic thiohydroxamate esters of type **6** do not undergo the Lossen rearrangement to yield isothiocyanates. Instead, nitrile sulfides **7** are produced which have been trapped with suitable dipolarophiles[9-11] (eq 3).



(3)

As a result of our studies of hydroxamate ester decompositions, we have obtained evidence which is consistent with the formation of nitrile oxides **8** as intermediates in some cases. Thus, the thermolysis of 5-substituted 1,3,2,4-dioxathiazole 2-oxides **3** in the presence of dimethyl acetylenedicarboxylate (DMADC) as a trapping agent produced mixtures of the corresponding isocyanates **2** and dimethyl 3-substituted isoxazole-4,5-dicarboxylates **9** (Scheme I).

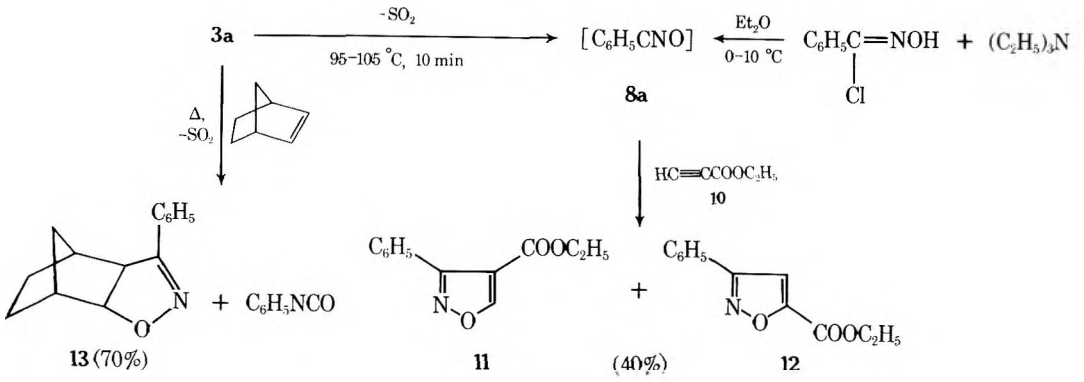
Scheme I



Compd	R	Yield, %[a] 2	9
a	C_6H_5-	55.5	39.3
b	4-$CH_3OC_6H_4-$	32	8
c	4-$O_2NC_6H_4-$		51.5
d	3,4-$Cl_2C_6H_3-$	36.2	57.5
e	n-$C_9H_{19}-$	(75)[b]	(25)[b]

[a] GC, C_6H_5Cl standard. [b] Relative weights by integration.

Scheme II



Products **2** and **9** were readily identified in the reaction mixtures by their GC–mass spectra. The isolated isoxazoles **9a–d** were identical in all respects with the authentic products (Table I) prepared from DMADC and the corresponding α-chloro oximes and triethylamine in ether.

Table I

6	R	Yield, % 9[a]	Mp, °C
a	C_6H_5–	46	52–54 (lit.[12] 62–63)
b	4-$CH_3OC_6H_4$–	73	72.5–73.5
c	4-$O_2NC_6H_4$–	45	103–105
d	3,4-$Cl_2C_6H_3$–	45	112.5–114
f	2,4,6-$(CH_3)_3C_6H_2$–	82	65.5–67

[a] Isolated yields of pure products from α-chloro oximes. All products gave satisfactory combustion analyses (C, H, N) and ir, NMR, and mass spectra.

Thermolysis of **3a** in excess ethyl propiolate **10** produced phenyl isocyanate and a mixture of the isomeric esters **11** and **12** (40% yield) in a mole ratio of 25:75 (Scheme II). The preponderant formation of isomer **12** is difficult to explain by ionic mechanisms and is strong evidence in support of the intermediate formation of benzonitrile oxide in this reaction. Treatment of excess **10** with benzonitrile oxide generated from α-chlorobenzaldoxime produced **11** and **12** in a mole ratio of 30:70, whereas the ratio of the corresponding methyl esters obtained from methyl propiolate is reported[13] to be 28:72. Esters **11** and **12** were easily separated by gas chromatography and identified by comparison of their spectra (ir, NMR, mass) with authentic materials.[14,15] Finally, the decomposition of **3a** in the presence of the more active dipolarophile norbornene produced adduct **13**[16] (mp 97–100 °C, mmp 98–100°) in good yield (Scheme II).

In contrast to **3a** and **3c** the dibenzohydroxamates **1a** and **1c** and excess DMADC did not yield 1,3-dipolar adducts when heated at the reflux temperature in chlorobenzene. The primary product in each case was the corresponding isocyanate.

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John E. Franz,* Helen K. Pearl

Monsanto Agricultural Products Company
Research Department
St. Louis, Missouri 63166

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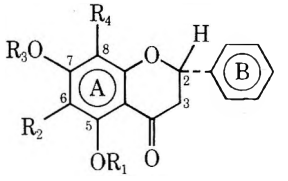
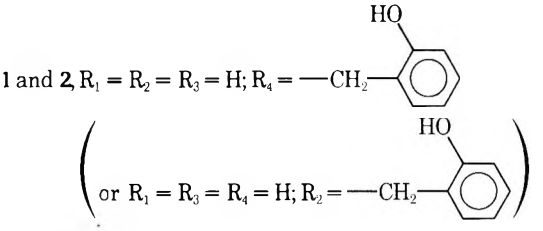
Uvaretin and Isouvaretin. Two Novel Cytotoxic *C*-Benzylflavanones from *Uvaria chamae* L.

Summary: Two cytotoxic principles, uvaretin (**1**) and isouvaretin (**2**), have been isolated from the stem bark of *Uvaria chamae* L. (Annonaceae) and their structures have been established as novel *C*-benzylflavanones.

Sir: An ethanolic extract of the stem bark of *Uvaria chamae* L. (Annonaceae) was found to show activity in vivo against P-388 leukemia in the mouse and in vitro against cells derived from human carcinoma of the nasopharynx (KB).[1] Fractionation of the ethanol extract was guided by assay against KB. The activity was concentrated in the ethyl acetate soluble fraction of an ethyl acetate–water partition. Chromatography of the ethyl acetate fraction over silicic acid afforded uvaretin and isouvaretin.

Uvaretin, $C_{22}H_{18}O_5$,[2] mp 210–211 °C, $[\alpha]^{25}D$ −52° (c 0.122, MeOH), gave a positive test (red) with magnesium–hydrochloric acid and formed a trimethyl ether upon treatment with excess ethereal CH_2N_2 for 4 days at room temperature. The uv spectrum of uvaretin showed λ_{max} (MeOH) 324 nm (ϵ 15 400) and 289 (10 500) and showed considerable bathochromic shifts with aluminum chloride (24 nm) sodium acetate[3] (36 nm) which are consistent with a flavanone nucleus with hydroxyl groups present at positions 5 and 7. The ir spectrum (KBr) showed broad hydroxyl bands at 3100 cm^{-1} and a carbonyl absorption at 1630 cm^{-1} which are in accord with the presence of a hydroxyl group at C-5 in a flavanone. The mass spectrum showed a parent peak at *m/e* 362 (100%) and fragment ions at *m/e* 285 (M^+ − 77, 16%), 258 (M^+ − 104, 37%), and 104 (9%) which indicated an unsubstituted B ring.[4,5]

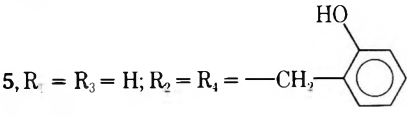




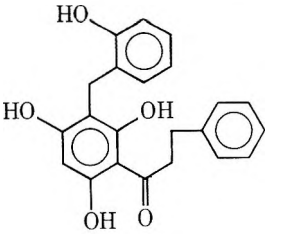
1 and **2**, $R_1 = R_2 = R_3 = H$; $R_4 = —CH_2$–(HO)

(or $R_1 = R_3 = R_4 = H$; $R_2 = —CH_2$–(HO))

3, $R_1 = R_2 = R_3 = R_4 = H$



5, $R_1 = R_3 = H$; $R_2 = R_4 = —CH_2$–(HO)



4

The NMR spectrum (60 MHz, acetone-d_6) clearly showed an ABX pattern characteristic of the protons at H-3 (AB) and H-2 (X) of a flavanone nucleus,[3] a 1 H singlet for H-6 (or H-8) at δ 6.10, a 5 H broad singlet for the five protons of ring B at δ 7.5, and a 1 H singlet at δ 12.60

for OH at C-5 (exchanges with D_2O). These features of the NMR spectrum are characteristic of flavanones like pinocembrin (3).[6] Additional peaks in the NMR spectrum of uvaretin include a 2 H singlet at δ 3.91, a 4 H multiplet near δ 6.8, and two other exchangeable protons located near the protons of the aromatic rings.

These data can be accommodated by a hydroxybenzyl substituent at C-6 (or C-8) in a 5,7-dihydroxyflavanone nucleus. The 4 H multiplet near δ 6.8 closely resembles the pattern found in *o*-hydroxybenzyl alcohol.[7]

Isouvaretin, $C_{22}H_{18}O_5$,[2] mp 215–217 °C, $[\alpha]^{25}D$ −15° (c 0.108, MeOH), also formed a trimethyl ether and had spectral data[8] very similar to that of uvaretin which led to the conclusion that isouvaretin and uvaretin were isomeric and differed only in the location of the hydroxybenzyl substituent. Catalytic hydrogenation of isouvaretin and uvaretin using H_2–Pd/C in ethanol containing KOH gave the same dihydrochalcone (4)[9] confirming the isomeric relationship.

C-Benzylation of (±)-pinocembrin (3)[10] using *o*-hydroxybenzyl alcohol and boron trifluoride etherate in dioxane[11] produced the two monobenzyl products (1 and 2) which were found to be identical[12] with uvaretin and isouvaretin and a dibenzyl product (5).[13]

The absolute stereochemistry of 1 and 2 follow from CD data which allows assignment of the 2*S* configuration.[14] Uvaretin and isouvaretin are the first reported examples of C-benzylflavanones.[15]

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References and Notes

(1) Tumor-inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute by procedures described in *Cancer Chemother. Rep., Part 3*, 3, 1 (1972). Uvaretin showed cytotoxicity (ED 50) against KB cell culture at 5.2 μg/ml and against PS cell culture at 17 μg/ml while isouvaretin was active at 2.7 μg/ml (KB) and 2.2 μg/ml (PS).

(2) The molecular formula was established by high resolution mass spectral data and supported by elemental analysis. For uvaretin and isouvaretin calculated *m/e* was 362.1154, found *m/e* 362.1169 and 362.1138, respectively.

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(7) The 60-MHz NMR spectra of *o*-, *m*-, and *p*-hydroxybenzyl alcohols were run in acetone-d_6 for comparison.

(8) Spectra: uv λ_{max} (MeOH) 324 nm (ϵ 12 500), 296 (9000), (NaOAc) 324; ir ν_{max} (KBr) 3030, 1650 cm^{-1}; NMR (60 MHz, acetone-d_6) δ 13.33 (1 H, s, exchanges D_2O) 7.50–7.84 (5 H), 6.67–7.50 (4 H), 6.26 (1 H, s), 5.68 (1 H, X of ABX), 4.00 (2 H, s), 2.67–3.60 (2 H, AB of ABX); *m/e* (rel abundance) 362 (100), 361 (9), 285 (13), 258 (22), 104 (13).

(9) **4** ($C_{22}H_{20}O_5$) had mp 207–208 °C; the formula was supported by high resolution MS. The products from the separate reductions were compared and found to be identical (melting points, mixture melting point, NMR, TLC, ir).

(10) Prepared according to the procedure described by S. Huzise and H. Tatsita, *Ber.*, **74B**, 275 (1941).

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(12) Melting point, mixture melting point (no depression), TLC, superimposible ir spectra.

(13) **5** had mp 118–120 °C; the formula ($C_{29}H_{24}O_6$) was supported by high resolutions MS. The spectral data was in accord with that expected for **5**.

(14) CD: **1**, $[\theta]_{355}$ +2260, $[\theta]_{314}$ +5080, $[\theta]_{288}$ −40 000, $[\theta]_{242}$ +3620, $[\theta]_{219}$ +34 600; **2**, $[\theta]_{328}$ +3800, $[\theta]_{289}$ −24 500, $[\theta]_{251}$ −2410, $[\theta]_{219}$ +29 600. The signs of the Cotton effects in the CD spectra of flavanones have been correlated with absolute stereochemistry: W. Gaffield, *Tetrahedron*, **26**, 4093 (1970).

(15) Studies are in progress to determine the location of the hydroxybenzyl substituent for each.

Charles D. Hufford,* William L. Lasswell, Jr.

Department of Pharmacognosy, School of Pharmacy University of Mississippi, University, Mississippi 38677

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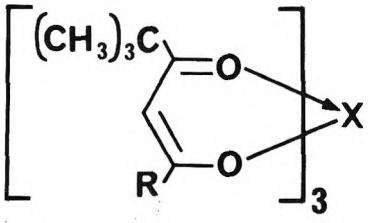
NMR Shift Reagents

Stretch your NMR



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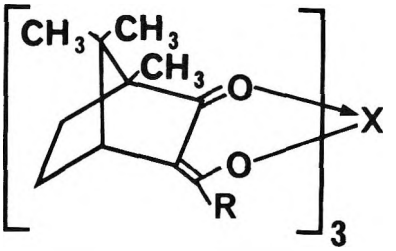
X = Pr (Resolve-Al Pr™)

R = n-C_3F_7; X = Eu (Resolve-Al EuFOD™)
X = Pr (Resolve-Al PrFOD™)

Since the initial report in 1969,[1] the study of lanthanide shift reagents has been one of the most active areas of chemistry to the extent that a 1973 review[2a] cites 488 references! These rare-earth chelates of β-diketones have become important to all users of nmr[2a,b] because of their ability to simplify complex spectra by causing spectacular changes in the chemical shifts of nuclei adjacent to an electronegative substituent. The **Resolve-Al™** reagents produce, with little line broadening, large changes in the chemical shifts of protons adjacent to hydroxyl, amine, oxime, aldehyde, ketone, ester, amide, ether, thioamide, sulfoxide, sulfone, nitrile and phosphate groups. The addition of **Resolve-Al™** or **Resolve-Al EuFOD™** as either a solid or a solution generally results in a downfield change in resonances whereas the reverse is true with **Resolve-Al Pr™** or **Resolve-Al PrFOD™**. In addition, correlation of observed changes in chemical shift with the geometry of the substrate-shift reagent complex has been used to make assignments of structure,[2] stereochemistry[2] and configuration.[2,3]

Polarimetry by NMR

Furthermore, rare-earth chelates of chiral β-diketones provide a convenient spectroscopic means[2a,b] to determine enantiomeric or optical purity without relying on difficult or time-consuming classical methods. The nmr spectra of chiral alcohols, amines, esters, ketones, sulfoxides and epoxides observed in the presence of **TFMC-Eu, TFMC-Pr** or **THFC-Eu** generally show such large chemical shift differences for the enantiotopic nuclei that the proportions of enantiomers can be measured directly by integration.[2a,b]



R = CF_3, X = Eu — **Tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium** (TFMC-Eu)

R = CF_3 X = Pr — **Tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]praseodymium** (TFMC-Pr)

R = n-C_3F_7, X = Eu — **Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium** (THFC-Eu)

References:

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