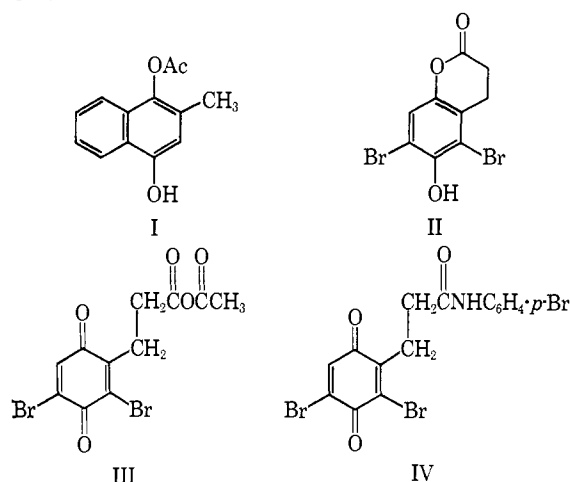


I, and the mixed anhydride III from the hydroquinone lactone II. Such observations may be of significance with respect to the mechanism of mitochondrial oxidative phosphorylation and the role of quinone cofactors therein.



Reaction of 2-methyl-1,4-naphthoquinone 1-acetate¹ with N-bromosuccinimide (2 equiv), in glacial acetic acid containing sodium acetate, leads rapidly to the formation of 2-bromo-3-methyl-1,4-naphthoquinone^{2a} (74% recovery) and acetic anhydride (98% recovery as *p*-bromoacetanilide). In an analogous manner, by oxidation of the hydroquinone lactone II³ with 1 equiv of N-bromosuccinimide the quinone carboxylic anhydride III is formed. Addition of *p*-bromoaniline to acetic acid solutions containing III results in nucleophilic attack at either carbonyl, *p*-bromoacetanilide being isolated in 62% yield. The quinone anilide IV, recovered in low yield, was identified by comparison with an authentic sample prepared by oxidation of the corresponding hydroquinone anilide. Control experiments show that, under the reaction conditions, *p*-bromoacetanilide formation does not occur in the absence of an oxidant.

Ultraviolet spectra of the reaction mixtures, following addition of oxidant and dilution with acetonitrile, correspond to those of quinones; thus, in the case of I, the spectrum is superimposable with that of authentic 2-bromo-3-methyl-1,4-naphthoquinone ($\lambda_{\max}^{\text{CH}_3\text{CN}}$ 245, 251, and 280 m μ); in the case of II, the spectrum is very similar to that of 2,6-dibromoquinone ($\lambda_{\max}^{\text{CH}_3\text{CN}}$ 288 m μ).⁴ There is no evidence from the spectroscopic data for bromo or acetoxy dienone intermediates.

Although mechanistic experiments have not been completed, it seems likely that the reactions leading to anhydride formation proceed by nucleophilic or solvolytic attack of acetate on an oxidatively generated acylium ion, as a real or transition-state intermediate. Survival of the phenolic oxygen in such a pathway would be in accord with the results of recent isotope experiments.⁵

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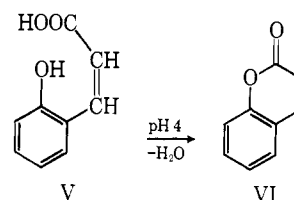
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The possible formation of hydroquinone monoesters in biological systems is a matter of concern with respect to energy production and utilization. It is conceivable that a species such as the reduced form of ubiquinone might be bound tightly to an enzyme, bringing a phenolic group close to a *protein* carboxyl. That the normally difficult esterification of a phenol may be facilitated, under the unimolecular and sterically constrained conditions of enzyme-substrate interaction,⁶ is exemplified by the formation of a lactone such as VI from the corresponding phenolic acid V. We have found that VI hydrolyzes at 25° in 0.0067 *M*



potassium hydroxide (10% acetonitrile) with a half-life of 4.3 min; upon acidification of the solution to pH 4.0 with acetic acid, VI is regenerated with a half-life of 26.6 min. The rates of these transformations are readily determined from the ultraviolet spectral changes.

In the oxidation of hydroquinone monophosphates, energy conservation is achieved by cleavage of a phosphorus-oxygen bond and generation of the metaphosphate species.^{2,4,7} Our experiments show that an analogous pathway is available for the oxidation of hydroquinone monocarboxylic esters, utilizing an acylium ion intermediate. Since acid anhydrides are isoenergetic with and convertible into acyl phosphates,⁸ the coupling of oxidation and phosphorylation by discrete steps has been demonstrated. Furthermore, it is currently held that *nonphosphorylated* high-energy intermediates, $\sim\text{C}$, are critically important species in mitochondrial oxidative phosphorylation.⁹

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(10) Staff Fellow, National Institutes of Health.

John W. Thanassi,¹⁰ Louis A. Cohen

Laboratory of Chemistry
National Institute of Arthritis and Metabolic Diseases
National Institutes of Health, Bethesda, Maryland

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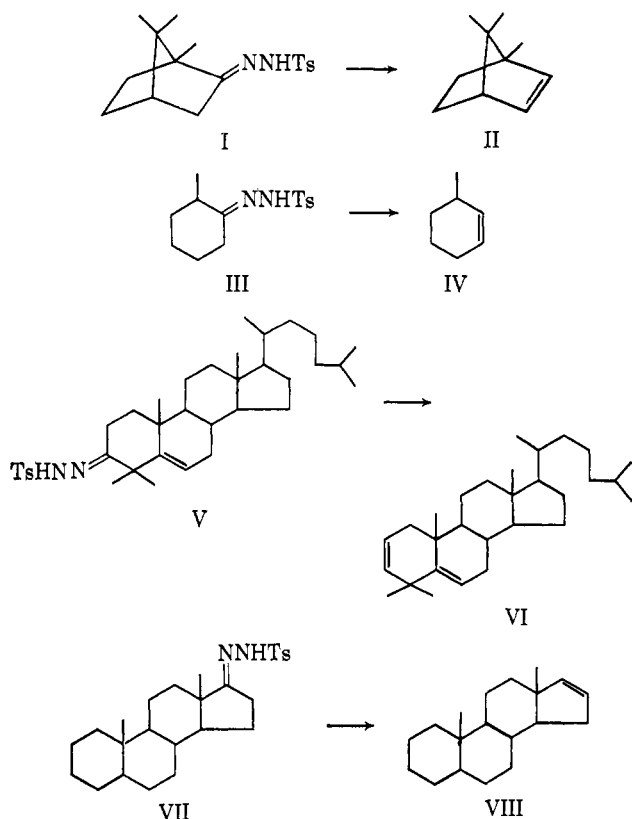
Tosylhydrazones. V.¹ Reaction of Tosylhydrazones with Alkylolithium Reagents. A New Olefin Synthesis

Sir:

We wish to report that aliphatic tosylhydrazones, containing an α -hydrogen, react with alkylolithium reagents to yield olefins, many of which may be difficult to prepare

(1) Tosylhydrazones. IV: R. H. Shapiro and J. H. Duncan, submitted for publication.

by other means. For example, camphor tosylhydrazone (I) reacts with 2 or more equiv of methyl lithium in ether or *n*-butyllithium in hexane to give a quantitative yield of 2-bornene (II). 2-Methylcyclohexanone tosylhydrazone (III) yields >98% 3-methylcyclohexene (IV) (<2% 1-methylcyclohexene), 4,4-dimethyl- Δ^5 -cholesten-3-one tosylhydrazone (V) yields 4,4-dimethyl- $\Delta^{2,5}$ -cholestadiene (VI), and androstan-17-one tosylhydrazone (VII) yields Δ^{16} -androstene (VIII), the latter two reactions proceeding quantitatively.² Although these olefins can be prepared by other routes, none can be prepared with the facility that this method offers. Since the formation of tosylhydrazones is essentially quantitative from the corresponding ketone, the two-step procedure leads to a high purity olefin in excellent yield.



The typical procedure involves dissolving or suspending the tosylhydrazone in dry ether or hexane and slowly adding >2 equiv of the alkyllithium at room temperature.³ Water is then added, the layers are separated, and the olefin is isolated by standard procedures.

The reaction appears to proceed *via* a carbanion intermediate. The reaction of I with *n*-butyllithium followed by treatment of the reaction mixture with D_2O led to the incorporation of one deuterium atom in the resulting 2-bornene. The deuterium atom was shown to be attached to C-2 by comparison of the nmr spectra of authentic 2-bornene and the reaction product. The vinylic region of the spectrum of II is characterized by a one-proton doublet ($J = 6$ cps) at 5.62 ppm and a one-proton approximate quartet at 5.85 ppm. The former signal was absent in the spectrum of the labeled 2-bornene and the signal at 5.85 ppm became a doublet. It is

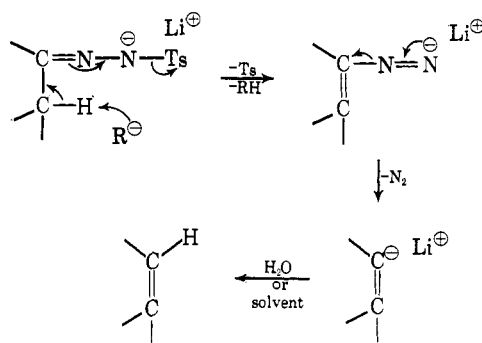
(2) All reaction products were determined by direct comparison with authentic specimens.

(3) The reaction proceeds smoothly at even -20° and therefore the method may be applicable to relatively volatile or sensitive olefins.

interesting to note that only a small amount of deuterium ($\sim 10\%$) was incorporated into 2-bornene in the reaction of I with methyl lithium in ether followed by D_2O treatment whereas the Δ^{16} -androstene obtained from VII under the same conditions contained 60% d_1 . Apparently the ether can act as a proton donor to varying extents depending on the system.⁴ In some cases we were able to identify ethanol in the reaction mixture, and quantitative gas determinations showed that 3.2–3.8 equiv of gas was evolved instead of the calculated 3 equiv. Camphor-3,3- d_2 tosylhydrazone⁵ gives 2-bornene-3- d_1 upon treatment with alkyllithium reagents. The position of the deuterium atom was proved by the nmr spectrum in which the signal at 5.85 ppm was absent and the signal at 5.62 ppm became a singlet.

Carbanion mechanisms have been previously proposed for base-induced tosylhydrazone decompositions,^{6,7} and Scheme I is consistent with our results.

Scheme I



It appears that the alkyl anion prefers to approach the least hindered position as well as to remove the more acidic hydrogen. We are presently carrying out experiments to explore the steric and electronic requirements of the reaction.

The reaction of tosylhydrazones with aromatic tosylhydrazones which do not contain α -hydrogens results in nucleophilic substitution. For example, the reaction of methyl lithium (1 equiv) with fluorenone tosylhydrazone results in the quantitative formation of 9-methylfluorene.⁸ 1-Indanone tosylhydrazone, which contains two α -hydrogens, gives a mixture of indene (elimination product) and 1-methylindan (nucleophilic substitution product), with the former predominating.

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(8) Many similar systems have been investigated. These results will appear in a future publication.

(9) National Science Foundation Undergraduate Research Participant.

Robert H. Shapiro, Marsha J. Heath⁹
Department of Chemistry, University of Colorado
Boulder, Colorado 80302

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