VOLUME 43 FEBRUARY 3, 1978 NUMBER 3 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

13593 **(-)-N-Benzyl-N-methylephedrinium bromide purum** >99%(Br); MP 209-211°; $[\alpha]_{546}^{20}$ -6.0±0.5° (c=4.5 in methanol)
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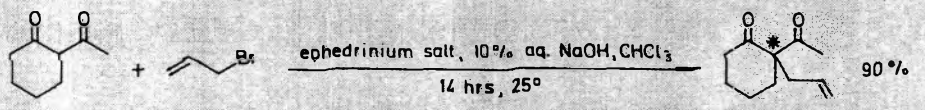
"Chiral phase transfer catalyst for asymmetric alkylation reactions": J.C. Fiaud, Tetrahedron Lett. (1975) 3495; L. Fieser, M. Fieser: "Reagents for Organic Synthesis", 6, 39; John Wiley and Sons, Inc.



40235 **(-)-N,N-Dimethylephedrinium bromide purum** >98%(Br); MP 236-238° (Trimethyl[1R,2S]-2-hydroxy-1-methyl-2-phenylethylammonium bromide)
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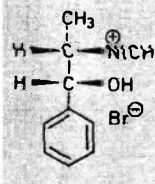

"Chiral phase-transfer catalyst": T. Hijama, T. Mishima, H. Sawada, T. Nozaki, J.Am.Chem.Soc. (1974) 97, 1627; L. Fieser, M. Fieser: "Reagents for Organic Synthesis", 6, 219; John Wiley and Sons, Inc.; "Chiral supporting electrolyte: D. Brown, L. Horner, Liebigs Ann.Chem. (1977) 77; W.J.M. van Tilborg, C.J. Smit, Tetrahedron Lett. (1977) 3651; Enantioselective electroreduction of Schiff's bases using optically active supporting electrolytes: L. Horner, D.H. Skaletz, Liebigs Ann.Chem. (1977) 1365

44220 **(-)-N-Dodecyl-N-methylephedrinium bromide, (-)MDEB purum** >98%(Br); MP 105-106° $[\alpha]_{546}^{20}$ -14.9±1° (c=1 in $CHCl_3$)
$C_{23}H_{42}BrNO$ MW 428.50

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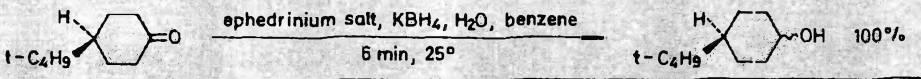
"Specific catalyst for the borohydride reduction of carbonyl compounds under phase-transfer conditions": S. Colonna, R. Fornasier, Synthesis (1975) 531; "Catalyst for the asymmetric reduction of ketones by phase transfer catalyses": J.P. Massé, E.R. Parayre, J.Chem.Soc.Chem.Comm. (1976) 438; "Catalyst for the stereospecific micellar hydrolysis of esters": C.A. Bunton et al., Tetrahedron Lett. (1971) 121; L. Fieser, M. Fieser: "Reagents for Organic Synthesis", 6, 249; John Wiley and Sons, Inc.



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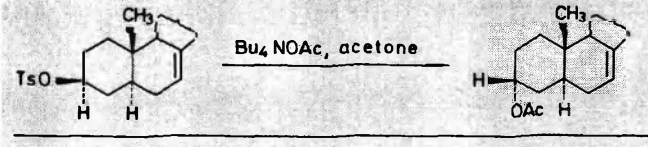

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Thermal and base-catalyzed rearrangement: A.G. Brook et al., J.Am.Chem.Soc. (1968) 90, 3876;
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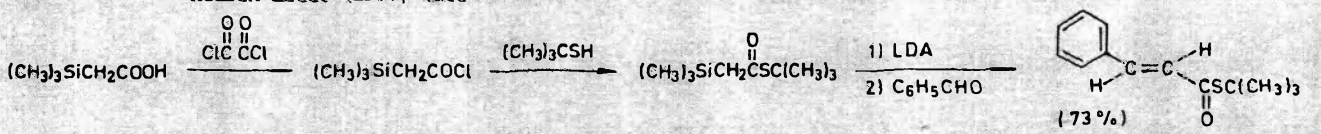
"A highly stereoselective condensation process for the conversion of carbonyl compounds to α,β-unsaturated thiol esters": D.H. Lucast and T. Wemple, Tetrahedron Lett. (1977) 1103



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THE JOURNAL OF Organic Chemistry

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

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Notice to Authors last printed in the issue of January 6, 1978

JOCEAH 43(3) 381–528 (1978)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

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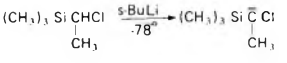
EPOXYSILANES IN SYNTHETIC ORGANIC CHEMISTRY

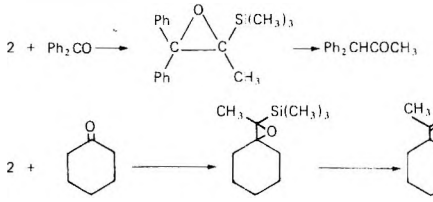
Significant advances have recently been made in the application of organosilicon compounds to organic syntheses using α,β-epoxytrimethylsilanes. These are derived from carbanions generated from chloroalkyltrimethylsilanes.

α-Chloroethyltrimethylsilane (1) gives the carbanion (2) when treated with s-BuLi in THF at -78°.[1]

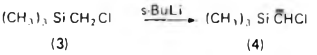


(1) (2)

Reaction of the carbanion with a carbonyl compound gives the α,β-epoxysilane which can be hydrolyzed to the corresponding methylketone in good yields. e.g.

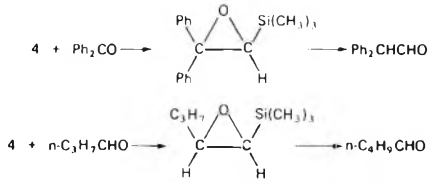


Chloromethyltrimethylsilane (3) gives the anion (4) with s-BuLi.[2]



(3) (4)

Homologous aldehydes are obtained when (4) is treated with carbonyl compounds and the intermediate α,β-epoxysilanes hydrolyzed. e.g.



The references report a wide variety of carbonyl compounds which undergo these reactions including aliphatic, aromatic and steroidal substrates.

The α,β-epoxysilanes, besides being precursors to homologous carbonyl compounds are convenient intermediates in the syntheses of stereospecific olefins via β-hydroxysilanes,[3] vinyl ethers, bromides and enamides.[4] The simplest α,β-epoxysilane, epoxyethyltrimethylsilane, can be prepared from vinyltrimethylsilane by reaction with perphthalic acid.[5]

α-Chloroethyltrimethylsilane (1) and chloromethyltrimethylsilane (3), precursors to the epoxysilane intermediates are both available from PCR.

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VOLUME 43, NUMBER 3

FEBRUARY 3, 1978

Intramolecular Dipolar Cycloaddition Reactions with Vinylbiphenyl-Substituted 1,3-Dipoles[1]

Albert Padwa,* Hao Ku, and Arthur Mazzu

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

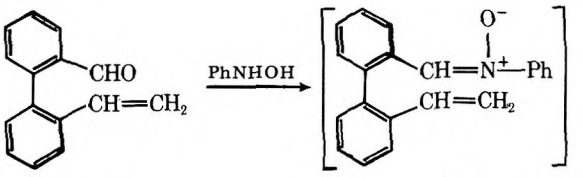
Received July 14, 1977

The intramolecular 1,3-dipolar cycloaddition reactions of several vinylbiphenyl-substituted 1,3-dipoles were studied. Condensation of 2′-vinyl-2-biphenylcarboxaldehyde with *N*-phenylhydroxylamine produced a transient nitrone intermediate which quantitatively cyclized to give phenanthro[9,10-*c*]isoxazole **5**. The regioselectivity of the above cycloaddition is controlled by steric factors and not by HOMO–LUMO interactions. A series of vinylbiphenyl-substituted 2*H*-azirines containing dipolarophile groups in close proximity to the azirine ring were subjected to UV irradiation. The exclusive formation of internal 1,3-dipolar cycloadducts can be attributed to cycloaddition of the initially generated nitrile ylide onto the neighboring double bond of the dipolarophile. A similar mode of cycloaddition occurred when *N*-(*p*-nitrobenzyl)-2′-vinyl-2-biphenylcarboximidoyl chloride (**26**) was treated with base. With these systems there is no particular constraint to attaining the parallel plane approach of addends, and consequently smooth 1,3-dipolar cycloaddition readily occurs. Irradiation of 3,3′-(2,2′-biphenylene)bis[2*H*-azirine] (**18**) with electron-deficient olefins gives cycloadducts derived from a transient diazabicyclo[3.1.0]hexene intermediate. The isolation of imidazole derivative **29** from the irradiation of **18** in the presence of dimethyl fumarate requires the formation of a discrete intermediate, in which transfer of a hydrogen from the ring to the side chain can occur. This process represents a rare example of an ene-type reaction from a 1,3-dipole.

Interest in the chemistry of 2*H*-azirines has increased considerably over the past several years.[2] As a synthetic reagent the 2*H*-azirine ring occupies a position of particular utility. An unusual feature of this three-membered heterocyclic ring is that it is susceptible to attack by both electrophilic and nucleophilic reagents.[2] In addition, the 2π electrons present in the ring can participate in thermally allowed [π4s + π2s] cycloadditions as dienophiles[3,4] or as dipolarophiles.[5] Few reactions rival cycloadditions in the number of bonds that undergo transformation during the reaction, producing products considerably more complex than the reactants. Cycloaddition reactions utilizing 2*H*-arizines include thermal reactions with ketenes,[6,7] ketenimines,[7] nitrile oxides,[5] cyclopentadienones,[8,9] cyclopentadiene,[10] diphenylisobenzofuran[11,12] and diazomethane[5] to yield a variety of unusual heterocyclic ring systems. 2*H*-Azirines also react photochemically with various carbon–carbon and hetero double bonds to give five-membered heterocyclic rings.[13,14] The photoreaction proceeds by way of irreversible opening of the azirine ring to form a nitrile ylide intermediate which is subsequently trapped by a suitable dipolarophile.[13] As part of a research program designed to uncover new cycloaddition reactions of 2*H*-azirines, we initiated a study dealing with the intramolecular cycloaddition reactions of nitrile ylides generated by the photolysis of 2*H*-azirines.[15] In a continuation of these studies, we have recently examined the intramolecular 1,3-dipolar cycloaddition reactions of a series of vinylbiphenyl-substituted 2*H*-azirines. The results which we have encountered with this system are described in this paper.

Results and Discussion

Our initial goal was to determine whether a vinylbiphenyl-substituted 1,3-dipole is capable of undergoing intramolecular 1,3-dipolar cycloaddition. For various reasons, nitrone **4** was chosen as a suitable substrate for our model studies. The preparation of *N*-[o-(*o*-vinylphenyl)benzylidene]aniline *N*-oxide (**4**) required the initial synthesis of 2′-vinyl-2-biphenylcarboxaldehyde (**3**). This was accomplished by treating diphenylaldehydic acid methyl ester (**1**)[16] with methyltriphenylphosphorane. Subsequent reduction of the initially formed Wittig product **2** with lithium aluminum hydride followed by oxidation of the resulting alcohol with Corey's pyridinium chlorochromate reagent[17] gave **3** in ex-



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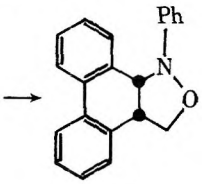

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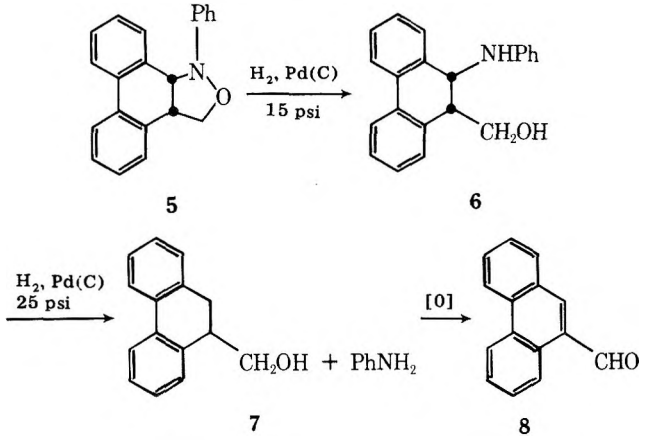
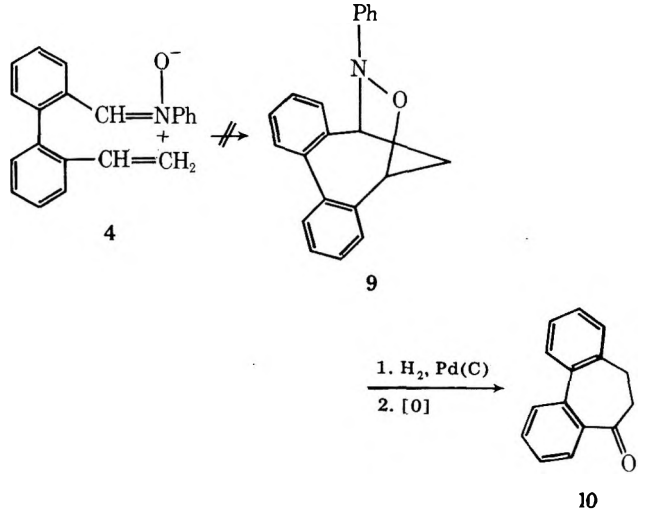
cellent yield. Condensation of **3** with *N*-phenylhydroxylamine in absolute ethanol resulted in the transient formation of **4** which immediately cyclized to give *cis*-1,3,3a,11b-tetrahydro-1-phenylphenanthro[9,10-*c*]isoxazole (**5**) as the only detectable product.

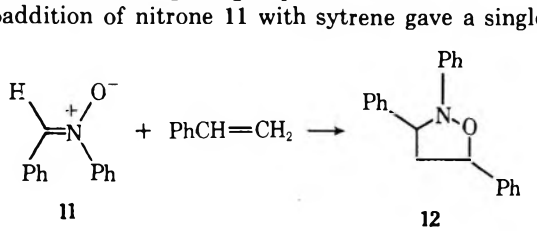
The regioselectivity of the internal cycloaddition was established by hydrogenolysis of **5** to **6** which, in turn, was further hydrogenated to **7**. Oxidation of **7** with pyridinium chlorochromate gave 9-phenanthrene carboxyaldehyde **8**. Thus, the formation of **8** from this series of reactions provides



strong support for the structure of **5**. If the internal cycloaddition of nitrone **4** had proceeded in the opposite direction (i.e., formation of **9**), then the hydrogenation oxidation sequence would have given ketone **10** as the ultimate product.

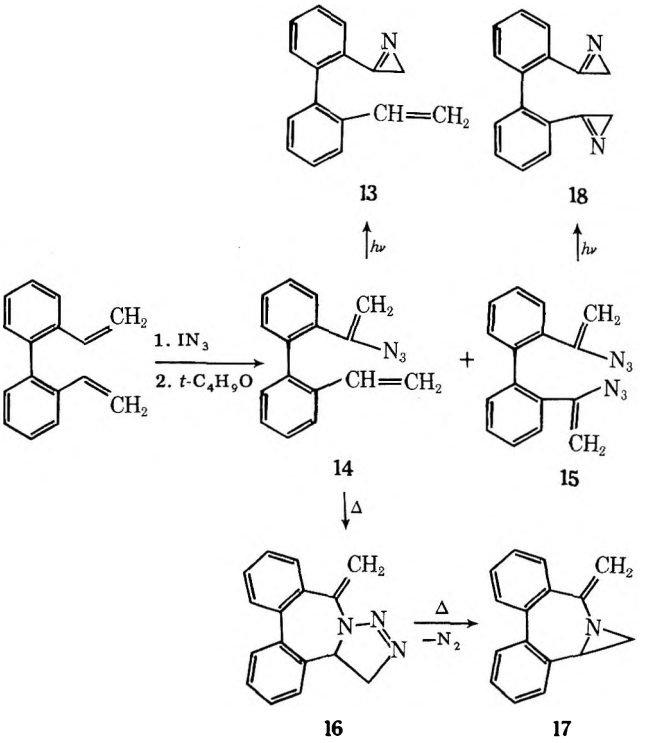


The formation of **5** from **4** is representative of the well-known intramolecular cycloaddition of a nitrone to an olefin.[18,19] Numerous examples of this type of cycloaddition exist in the literature.[19,20] LeBel and co-workers have elegantly demonstrated the utility and synthetic scope of this intramolecular dipolar cycloaddition for the preparation of a variety of polycyclic isoxazolidines.[21] The exclusive formation of **5** is especially interesting in light of Huisgen's work dealing with the bimolecular reaction of *N*-phenylbenzalnitrone (**11**) with styrene.[22] Huisgen's group was able to show that the cycloaddition of nitrone **11** with sytrene gave a single regioisomer whose structure was established as isoxazolidine **12**. Thus, the regioselectivity observed in the reaction of **3** with *N*-phenylhydroxylamine is directly opposite to that encountered by Huisgen. Preferential formation of **5** rather than **9** by a concerted pathway may be due to steric destabilization of the transition state for formation of the latter. It would seem as though the regioselectivity of the intramolecular cycloaddition of nitrone **4** is controlled by steric factors and not by the HOMO–LUMO interaction, which generally control the regioselectivity in bimolecular cycloaddition reactions.[23-25]

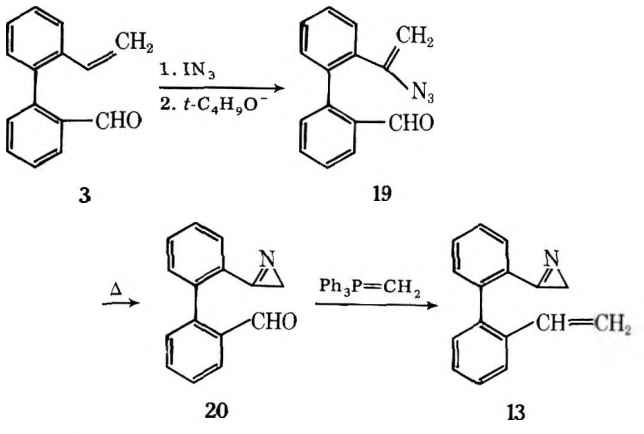


Having established the occurrence of an intramolecular 1,3-dipolar cycloaddition reaction with vinylbiphenyl nitrone **4**, we decided to study the intramolecular photocycloaddition reactions of some related vinylbiphenyl substituted 2*H*-azirines. Irradiation of 2*H*-azirines generates nitrile ylides as reactive intermediates which can undergo both 1,1- and 1,3-intramolecular dipolar cycloaddition.[15] As was pointed out elsewhere,[15] the geometry of the transition state involved in the intramolecular 1,1-cycloaddition reaction is significantly different from that required for concerted 1,3-dipolar cycloaddition. In view of the stringent spatial requirements associated with the intramolecular cycloaddition of nitrile ylides, we thought it worthwhile to examine the photochemical behavior of a series of vinylbiphenyl-substituted 2*H*-azirines in order to determine whether a 1,1- or 1,3-dipolar cycloaddition would occur.

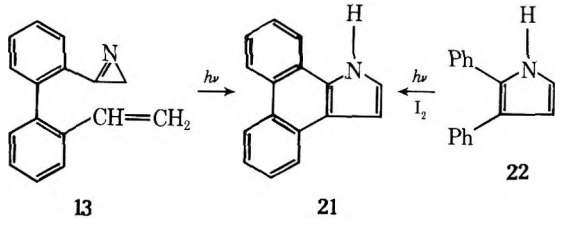
As our first model, we chose to investigate the photochemistry of 3-(2′-vinyl-2-biphenyl)-2*H*-azirine (**13**). Our initial attempt to synthesize **13** involved the classical iodine azide route of Hassner and co-workers.[26] Reaction of 1.1 equiv of iodine azide with 2,2′-divinylbiphenyl followed by treatment of the initially formed iodine azide adducts with potassium *tert*-butoxide resulted in the formation of a mixture of both the monoazide **14** and divinylazide **15**. It would appear as though the initially formed iodine azide adduct undergoes further reaction with IN_3 at a rate competitive with starting material. Monoazide **14** was found to rapidly cyclize to triazolo[1,5-*a*]azepine **16** on standing at room temperature.[27] Further heating of **16** resulted in the loss of nitrogen and formation of vinylaziridine **17**. Since it was not possible to obtain a sample of **13** from the thermolysis of vinyl azide **14**, we subjected the mixture of vinyl azides (i.e., **14** and **15**) to UV



irradiation. Chromatography of the crude photolysate resulted in the isolation of the desired 2*H*-azirine **13** in 13% yield as well as bis(2*H*-azirine) **18** in 60% overall yield. Since the yield of **13** was so low, we decided to use an alternate procedure to prepare azirine **13.** This was accomplished by treating aldehyde **3** with iodine azide followed by reaction with potassium *tert*-butoxide to give **19** in high yield. Thermolysis of this material in refluxing benzene gave 2′-(2*H*-azirin-3-yl)-2-biphenylcarboxaldehyde (**20**) in 85% yield. Treatment of the azirinyl aldehyde with methyltriphenylphosphorane afforded the desired 3-(2′-vinyl-2-biphenyl)-2*H*-azirine (**13**) in good yield.

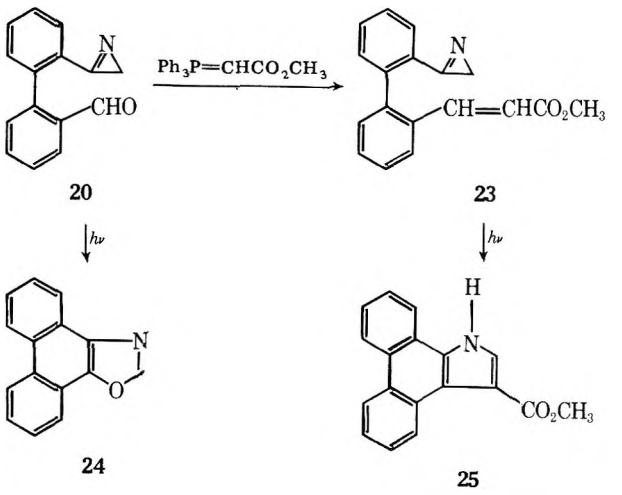


Irradiation of azirine **13** in benzene gave 1*H*-phenanthro[9,10-*b*]pyrrole (**21**) as the only identifiable photoproduct. The formation of this material arises by 1,3-dipolar cycloaddition of the initially formed nitrile ylide onto the double bond followed by air oxidation to pyrrole **21.** No detectable quantities of a 1,1-cycloadduct could be found in the crude photolysate. The structure of **21** was unequivocally established by comparison with an independently synthesized sample obtained by the iodine-catalyzed photooxidation of 2,3-diphenylpyrrole (**22**). Rigidly held stilbene moieties are



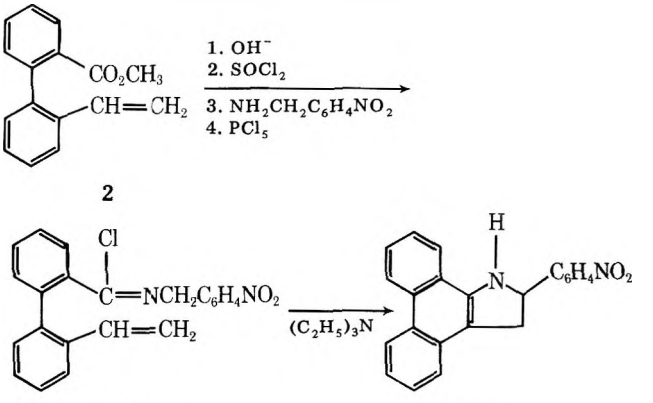
known to yield phenanthrene derivatives on irradiation and provide excellent precedent for this latter transformation.[28-31]

Additional examples of the intramolecular 1,3-dipolar cycloaddition reaction of these vinylbiphenyl-substituted systems were provided by the photolysis of azirines **20** and **23.** Methyl 2′-(2*H*-azirin-3-yl)-2-biphenylacrylate (**23**) was conveniently prepared by treating azirinyl aldehyde **20** with carbomethoxymethyltriphenylphosphorane. Irradiation of **23** in benzene gave methyl 1*H*-dibenz[*e*,*g*]indole-3-carboxylate **25** in 43% yield. Again, no detectable quantities of a 1,1-cycloadduct could be found in the crude photolysate. Similarly, irradiation of azirinyl aldehyde **20** gave phenanthro[9,10-*d*]oxazole (**24**) as the sole photoproduct. The structure of this material was verified by comparison with an independently synthesized sample prepared by the iodine-catalyzed photooxidation of 4,5-diphenyloxazole.[32] The formation of both of these adducts can be attributed to 1,3-dipolar addition of the initially generated nitrile ylide onto the adjacent π bond followed by air oxidation. The regioselectivity encountered here is similar to that normally observed in the



photolysis of 2*H*-azirines with benzaldehyde and methyl acrylate.[13,14]

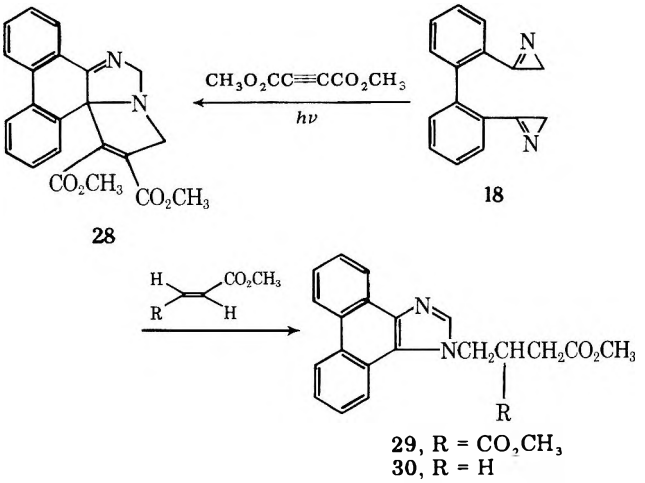
We also studied the intramolecular dipolar cycloaddition reaction of the nitrile ylide generated from the base treatment of imidoyl chloride **26.** o-Vinylbiphenyl-substituted imidoyl chloride **26** was conveniently prepared by the series of reactions outlined below. Reaction of triethylamine with a benzene solution of **26** at room temperature produced triethylammonium chloride and an orange-red solution, which presumably contains the unstable nitrile ylide.[33] After stirring for 20 h at room temperature, an orange solid was obtained whose structure was identified as 2,3-dihydro-2-(*p*-nitrophenyl)-1*H*-phenanthro[9,10-*b*]pyrrole (**27**). The formation of **27** can be attributed to 1,3-dipolar addition of the initially generated nitrile ylide across the neighboring double bond followed by a rapid 1,3-H shift. The complete absence of a 1,1-cycloadduct with this system indicates that the transition state involved in the cycloaddition must be flexible enough to allow for maximum orbital overlap in the normal "two-plane" orientation approach required for 1,3-dipolar cycloaddition.[34]



Having verified that vinylbiphenyl-substituted 2*H*-azirines undergo smooth intramolecular 1,3-dipolar cycloaddition, we turned our attention to the photochemical behavior of bis(2*H*-azirine) **18.** Previous work has shown that 2*H*-azirines can be converted to 1,3-diazabicyclo[3.1.0]hex-3-enes when the irradiation is carried out in the absence of an added dipolarophile.[35,36] The formation of these dimers can be rationalized by 1,3-dipolar addition of the initially generated nitrile ylide onto a ground-state azirine molecule. Care is required in the choice of solvent, photolysis time, and substituents since the 1,3-diazabicyclohexenes are themselves photochemically labile.[37] On the basis of these earlier observations, we felt that the irradiation of a representative bis(2*H*-azirine) such as **18** could lead to some interesting photochemistry.

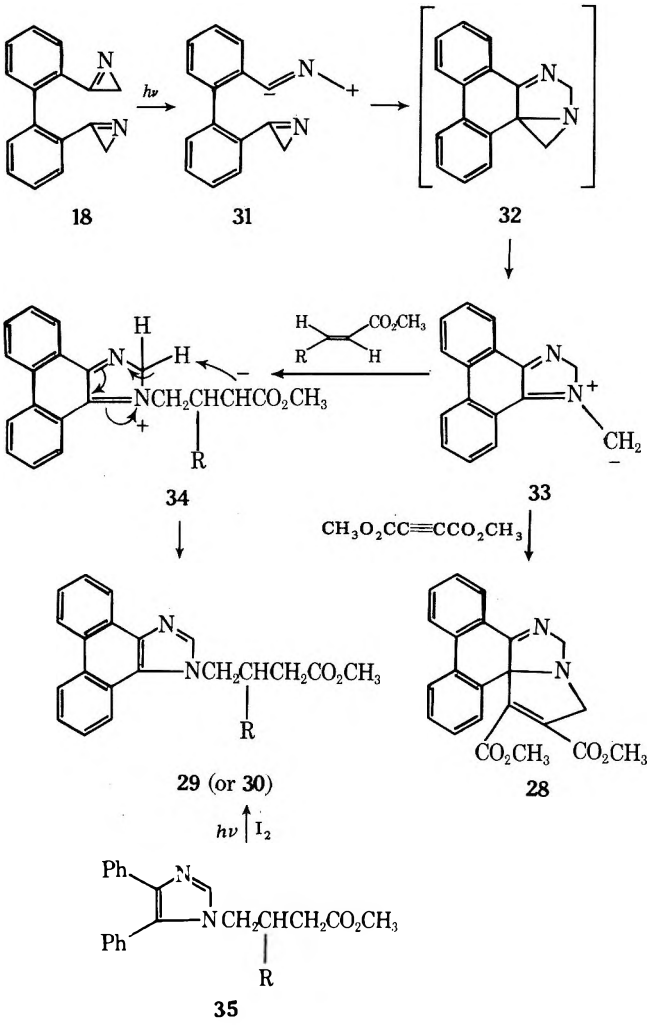
Irradiation of 3,3′-(2,2′-biphenylene)bis[2*H*-azirine] (**18**) in benzene through Pyrex resulted in the formation of a complex mixture of products. However, when the irradiation of **18** was carried out in the presence of dimethyl acetylenedicarboxylate a good yield of a cycloadduct **28** was obtained. The structure of this material was assigned as dimethyl 2*H*,4*H*-phenanthro[9,10-*d*]pyrrolo[1,2-c]imidazole-5,6-dicarboxylate (**28**) on the basis of its characteristic analytical and spectral data. Photolysis of **18** with dimethyl fumarate in benzene took an entirely different course and produced cycloadduct **29** as the only detectable photoproduct. The structure of this material was verified by comparison with an independently synthesized sample prepared from the reaction of 4,5-diphenylimidazole with dimethyl itaconate followed by an iodine-induced photooxidation of the imidazole ring of structure **35**. In an analogous manner, photoaddition of **18** with methyl acrylate gave phenanthroimidazole **30** in high yield.

The formation of cycloadduct **28** can be rationalized by the assumption that the initially generated nitrile ylide (i.e., **31**)



undergoes rapid cycloaddition across the C–N double bond of the adjacent azirine ring to give a transient diazabicyclohexene **32**. The high degree of order already present in the transition state undoubtedly enhances the rate of the intramolecular reaction relative to bimolecular cycloaddition with the added dimethyl acetylenedicarboxylate. The initially generated diazabicyclohexene **32** undergoes a subsequent ring opening to give azomethine ylide **33** which is ultimately trapped with the added dipolarophile. Reactions involving the photochemical cleavage of bicycloaziridines to azomethine ylides[37] and their subsequent additions to reactive multiple bonds are well known and provide good chemical analogy for the above suggestion.

The isolation of cycloadduct **29** (or **30**) from the addition of dimethyl fumarate to azomethine ylide **33** seemingly requires the formation of a discrete intermediate (i.e., **34**) in which transfer of a hydrogen from the ring to the side chain can occur. The results do not seem to be consistent with a process involving 1,3-cycloaddition of **33** with dimethyl fumarate followed by ring opening of the initially formed cycloadduct to give **29**, since there is no reason why the cycloadduct derived from methyl acrylate would be expected to give **30** under the reaction conditions used. The formation of cycloadducts **29** and/or **30** in the reaction of **18** with electron-deficient olefins has some interesting implications in relation to the classical 1,3-dipolar cycloaddition reaction.[25] Current opinion favors a concerted mechanism for dipolar cycloaddition,[25] although an alternate proposal involving a spin-paired diradical intermediate has been advanced by Firestone.[38] The above data appear to provide a rare example of an ene-type reaction from a 1,3-dipole. The possibility that



other ene-reactions can occur from 1,3-dipoles now merits serious consideration. We are further investigating these mechanistic ramifications.

Experimental Section

All melting and boiling points are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. The infrared absorption spectra were determined on a Perkin-Elmer Model 137 Infracord spectrophotometer. The ultraviolet absorption spectra were measured with a Cary Model 14 recording spectrophotometer using 1-cm matched cells. The proton magnetic resonance spectra were determined at 100 MHz using a Jeolco-MH-100 and a XL-100 spectrometer. Mass spectra were determined with a Perkin-Elmer RMU6 mass spectrometer at an ionizing voltage of 70 eV. All irradiations were carried out using a 450-W Hanovia medium-pressure mercury arc.

Preparation of 2′-Vinyl-2-biphenylcarboxaldehyde (3). To a solution containing 25.0 g of methyltriphenylphosphonium bromide in 150 mL of dry ether was added 28.0 mL of a 2.5 M *n*-butyllithium solution at room temperature under a nitrogen atmosphere. The resulting orange solution was allowed to stir at room temperature for 20 min prior to the addition of 10.2 g of diphenaldehydic acid methyl ester (**1**)[16] in 200 mL of ether. The mixture was stirred at room temperature for 24 h and then 4 drops of water was added, and the solution was filtered to remove the precipitated triphenylphosphine oxide. Removal of the solvent under reduced pressure left a crude brown residue which was chromatographed on a 3 × 50 cm Florosil column using a 40% ether–pentane mixture as the eluent. The major component isolated was a pale oil, 5.0 g (49%), which was identified as 2′-vinyl-2-biphenylcarboxylic acid methyl ester (**2**) on the basis of the following spectral data: IR (neat) 3.39, 5.75, 6.22, 6.78, 6.95, 7.72, 8.82, 9.10, 10.90, 13.23, and 14.00 μm; NMR (60 MHz, $CDCl_3$) τ 6.50 (s, 3 H), 5.00 (dd, 1 H, J = 10.0 and 1.5 Hz), 4.49 (dd, 1 H, J = 18.0 and 1.5 Hz), 3.62 (dd, 1 H, J = 18.0 and 10.0), 2.41–2.99 (m, 7 H), and 2.03–2.26 (m, 1 H).

To a solution containing 360 mg of lithium aluminum hydride in 25 mL of dry ether was added to 4.0 g of the above ester in 25 mL of

ether. The mixture was heated at reflux for 1 h and cooled, and then 1 mL of a 10% sodium hydroxide solution was added dropwise followed by 2 mL of water. The ethereal solution was decanted from the gummy precipitate and washed with water, and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to leave behind 3.0 g (89%) of a clear oil which was assigned as 2′-vinyl-2-biphenylmethanol on the basis of the following spectral data: IR (neat) 2.95, 3.21, 6.10, 6.76, 6.90, 7.04, 8.32, 9.9, 10.90 and 13.22 μm; NMR (60 MHz, $CDCl_3$) τ 8.00 (s, 1 H), 5.71 (s, 2 H), 4.98 (dd, 1 H, J = 10.0 and 1.5 Hz), 4.48 (dd, 1 H, J = 18.0 and 1.5 Hz), 3.66 (dd, 1 H, J = 18.0 and 10.0 Hz), and 2.32–3.07 (m, 8 H). The crude alcohol was not purified but was used directly in the next step.

To a solution containing 2.16 g of pyridinium chlorochromate[17] in 25 mL of methylene chloride at room temperature was added 1.05 g of the above alcohol in 25 mL of methylene chloride. After stirring for 1.5 h, the mixture was filtered through silica gel to remove the chromium salts. The solvent was removed under reduced pressure to leave behind 900 mg (86%) of a pale-yellow oil whose structure was assigned as 2′-vinyl-2-biphenylcarboxaldehyde (**3**) on the basis of its spectral data: IR (neat) 3.28, 3.53, 3.64, 5.90, 6.24, 6.83, 6.95, 7.21, 7.99, 8.35, 10.05, 10.88, 12.05 and 13.21 μm; NMR (100 MHz, $CDCl_3$) τ 4.96 (d, 1 H, J = 11.0 Hz), 4.40 (d, 1 H, J = 16.0 Hz), 3.67 (dd, 1 H, J = 16.0 and 11.0 Hz), 2.33–2.98 (m, 7 H), 1.98–2.12 (m, 1 H), and 0.38 (s, 1 H).

Reaction of 2′-Vinyl-2-biphenylcarboxaldehyde with *N*-Phenylhydroxylamine. A solution containing 550 mg of *N*-phenylhydroxylamine and 1.04 g of **3** in 5 mL of ethanol was allowed to stand at room temperature for 4 h. At the end of this time, a pale-yellow oil had separated which eventually solidified. Recrystallization of the solid from chloroform–hexane gave 998 mg (66%) of 1,3,3a,11b-tetrahydro-1-phenylphenanthro[9,10-c]isoxazole (**5**): mp 147–149 °C; IR (KBr) 6.28, 6.77, 6.91, 8.26, 8.84, 9.26, 9.81, 10.25, 10.64, 11.13, 13.15, 13.61, and 14.34 μm; UV (methanol) 266 (ε 17 000) and 301 nm (ε 1710); NMR (100 MHz, $CDCl_3$) τ 6.12–6.61 (m, 2 H), 5.50 (dd, 1 H, J = 16.0 and 12.0 Hz), 4.86 (d, 1 H, J = 6.0 Hz), 2.52–3.11 (m, 11 H) and 2.13–2.36 (m, 2 H); mass spectrum *m/e* 299 (M^+), 269, 206, 205, 191, 179, 178 (base), 177, 176, and 93.

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.24; H, 5.72; N, 4.68. Found: C, 84.24; H, 5.76; N, 4.68.

Addition of $Eu(Fod)_3$ shift reagent to the NMR sample resulted in the conversion of the multiplet at 6.12–6.61 into a doublet of doublets of doublets (τ 6.63, 1 H, J = 7.0, 6.0, and 5.5 Hz) and a doublet of doublets (τ 6.32, 1 H, J = 9.0 and 7.0 Hz). The doublet of doublets at τ 5.50 was slightly compressed [τ 5.72 (dd, 1 H, J = 9.0 and 6.0 Hz)] and the doublet at τ 4.86 remained unchanged except for a slight downfield shift (τ 4.80).

The structure of this product was further verified by reduction with palladium on carbon. A 150-mg sample of **5** was taken up in methanol. To this solution was added 5 mg of a 5% palladium on carbon catalyst. The mixture was subjected to hydrogenolysis in a Parr hydrogenation apparatus at 15 psi for 5 h at room temperature. At the end of this time, the catalyst was filtered and the solvent removed under reduced pressure to give 65 mg (62%) of a pale oil which was identified as *10-anilino-9,10-dihydro-9-phenanthrenemethanol* (**6**) on the basis of its spectral properties: IR (neat) 2.94, 3.43, 6.21, 6.63, 6.88, 7.59, 8.43, 9.66, 10.93, 13.30, and 14.43 μm; NMR (100 MHz, $CDCl_3$) τ 6.63–6.83 (m, 1 H), 6.20–6.36 (m, 2 H), 5.05 (d, 1 H, J = 4.0 Hz), and 2.13–3.43 (m, 14 H). The amino alcohol **6** was further hydrogenated. A 60-mg sample of this material was taken up in methanol and 5 mg of 5% palladium on carbon was added. The mixture was subjected to hydrogenolysis in a Parr apparatus at 25 psi for 92 h at room temperature. At the end of this time the catalyst was filtered and the solvent removed under reduced pressure. The major component obtained was identified as 9,10-dihydro-9-phenanthrenemethanol (**7**) on the basis of its spectral data: IR (neat) 2.98, 3.41, 6.22, 6.71, 6.88, 9.31, 9.70 and 13.20 μm; NMR (100 MHz, $CDCl_3$) τ 8.31 (br s, 1 H), 6.84–7.18 (m, 3 H), 6.43–6.62 (m, 2 H), 2.60–2.92 (m, 5 H), and 2.11–2.50 (m, 3 H). The crude alcohol was oxidized using 100 mg of pyridinium chlorochromate[17] *in 25 mL of methylene chloride to give 9-phenanthrenecarboxyaldehyde* (**8**), mp 100–102 °C (lit.[39] mp 100–101 °C). The structure of this material was verified by comparison with an authentic sample.

Irradiation of 2-(1-Azidovinyl)-2′-vinylbiphenyl (14) in Benzene. A 90-mg sample of 2-(1-azidovinyl)-2′-vinylbiphenyl[27] (**14**) in 150 mL of distilled benzene was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a uranium glass filter sleeve for 70 min. The solvent was removed under reduced pressure and the crude photolysate was subjected to preparative thick-layer chromatography using a 1:1 mixture of pentane–ether as the eluent. The major band isolated from the thick-layer plate contained 65 mg (80%) of a pale oil which was identified as 3-(2′-vinyl-2-biphenyl)-2*H*-azirine (**13**) on the basis of the following spectral data: IR (neat) 3.27, 5.75, 6.14, 6.24, 6.80, 6.93, 7.60, 10.02, 10.91, and 13.07 μm; UV (cyclohexane) 300 nm (ε 2060); NMR (100 MHz $CDCl_3$) τ 8.73 (s, 2 H), 4.95 (d, 1 H, J = 12.0 Hz), 4.46 (d, 1 H, J = 18.0 Hz), 3.68 (dd, 1 H, J = 18.0 and 12.0 Hz), 2.33–2.95 (m, 7 H) and 1.93–2.07 (m, 1 H); mass spectrum *m/e* 219 (M^+), 218 (base), 217, 204, 191, 189, 179, and 178.

Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.52; H, 5.76; N, 6.48.

Preparation of 2′-(2*H*-Azirin-3-yl)-2-biphenylcarboxaldehyde (20). To a solution containing 3.26 g of sodium azide in 40 mL of acetonitrile at −5 °C was added a solution containing 3.57 g of iodine monochloride in 5 mL of acetonitrile. The mixture was allowed to stir for 30 min and then 3.34 g of 2′-vinyl-2-biphenylcarboxaldehyde (**3**) dissolved in 10 mL of acetonitrile was added. The mixture was stirred for an additional 30 min at −5 °C and was then stirred for 9 h at room temperature. The resulting orange slurry was added to 200 mL of water and then extracted with ether. The ether extracts were washed with a 5% aqueous sodium thiosulfate solution and then with water. The ethereal layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 5.51 g (93%) of an orange oil which was used immediately in the next step.

To a solution containing the above iodine azide adduct in 50 mL of dry ether at −5 °C was added 2.24 g of potassium *tert*-butoxide. The mixture was allowed to stir at 5 °C for 14 h, washed with water, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left 3.10 g (83%) of an orange oil which was identified as 2′-(1-azidovinyl)-2-biphenylcarboxaldehyde (**19**) on the basis of the following spectra characteristics: IR (neat) 3.50, 4.75, 5.88, 6.22, 7.73, 8.33, 11.10, 12.03, and 13.20 μm; NMR (60 MHz, $CDCl_3$) τ 5.31 (d, 1 H, J = 1.5 Hz), 5.29 (d, 1 H, J = 1.5 Hz), 2.42–2.90 (m, 7 H), 1.98–2.18 (m, 1 H), and 0.23 (s, 1 H). The crude oil was used directly in the next step without purification.

A solution containing 3.1 g of the above vinyl azide and 3 mg of 1,4-diazabicyclo[2.2.2]octane in 250 mL of benzene was heated at reflux for 20 h. The solvent was removed under reduced pressure, and the residue was purified by passing it through a 3 × 60 cm Florosil column using a 20% acetone–hexane solution as the eluent. Removal of the solvent under reduced pressure left 2.25 g (85%) of a yellow oil which was subsequently sublimed at 40 °C (0.05 mm) to give 2′-(2*H*-azirin-3-yl)-2-biphenylcarboxaldehyde (**20**) as a pale-yellow solid: mp 67–68 °C; IR (KBr) 3.26, 3.51, 5.75, 5.91, 6.28, 6.94, 7.14, 7.85, 8.33, 10.09, 12.0 and 12.95 μm; UV (cyclohexane) 295 (ε 3380) and 245 nm (ε 19 900); NMR (60 MHz, $CDCl_3$) τ 8.67 (s, 2 H), 1.77–2.68 (m, 8 H), and 0.37 (s, 1 H); mass spectrum *m/e* 221 (M^+), 205, 204, 192 (base), 191, and 165.

Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.37; H, 5.05; N, 6.10.

Preparation of 3-(2′-Vinyl-2-biphenyl)-2*H*-azirine (13). To a solution containing 1.43 g of methyltriphenylphosphonium bromide in 50 mL of dry ether was added 1.6 mL of a 2.5 M *n*-butyllithium solution at room temperature under a nitrogen atmosphere. The resulting orange solution was allowed to stir at room temperature for 20 min prior to the addition of 796 mg of 2′-(2*H*-azirin-3-yl)-2-biphenylcarboxaldehyde (**19**) in 30 mL of anhydrous ether. The mixture was allowed to stir at room temperature for 4 days and was then filtered to remove the precipitated triphenylphosphine oxide. Removal of the solvent under reduced pressure left a dark yellow oil which was chromatographed on a 2 × 30 cm Florosil column using a 1:1 pentane–ether mixture as the eluent. The major fraction isolated contained 356 mg (45%) of a pale oil which was identified as 3-(2′-vinyl-2-biphenyl)-2*H*-azirine (**13**). The spectral properties of this compound were identical to those obtained for the major product isolated from the irradiation of 2-(1-azidovinyl)-2′-vinylbiphenyl (**14**).

Irradiation of 3-(2′-Vinyl-2-biphenyl)-2*H*-azirine (13) in Benzene. A 280-mg sample of 3-(2′-vinyl-2-biphenyl)-2*H*-azirine (**13**) in 410 mL of distilled benzene was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Corex filter sleeve for 45 min. The solvent was removed under reduced pressure, and the crude residue was subjected to preparative thick-layer chromatography using a 1:1 pentane–ether mixture as the eluent. The major band isolated contained 123 mg (44%) of 1*H*-phenanthro[9,10-*b*]pyrrole (**21**) as a white solid: mp 155–156 °C; IR (KBr) 2.95, 6.16, 6.49 6.69, 6.88, 7.10, 8.03, 9.15, 11.10, 13.14, and 13.76 μm; UV (cyclohexane) 250 (ε 51 200), 255 (ε 77 600), 287 (ε 14 000), and 298 nm (ε 7440); NMR (60 MHz, $CDCl_3$) τ 2.80–3.04 (m, 2 H), 2.38–2.70 (m, 4 H), 2.06–2.36 (m, 1 H), 1.71–1.98 (m, 1 H), 1.25–1.50 (m, 2 H), and 0.90–1.20 (m, 1 H); mass spectrum *m/e* 218, 217 (M^+ and base), 187, 108.5 (M^{2+}), and 94.

Anal. Calcd for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.63; H, 4.98; N, 6.36.

The structure of this material was further established by comparison with an independently synthesized sample. A solution containing 75 mg of 2,3-diphenylpyrrole[40] (**22**) and 3 mg of iodine in 135 mL of cyclohexane was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Pyrex filter sleeve for 45 min. The solvent was removed under reduced pressure, and the crude photolysate was subjected to preparative thick-layer chromatography using a 20% ether–pentane mixture as the eluent. The major band isolated contained 31 mg (40%) of 1*H*-phenanthro[9,10-*b*]pyrrole (**21**): mp 155–156 °C. The spectral properties of this compound were identical to those obtained for the major product isolated from the irradiation of 3-(2′-vinyl-2-biphenyl)-2*H*-azirine (**13**).

Preparation of Methyl 2′-(2*H*-Azirin-3-yl)-2-biphenylacrylate (23). A solution containing 350 mg of 2′-(2*H*-azirin-3-yl)-2-biphenylcarboxaldehyde (**20**) and 560 mg of carbomethoxymethyltriphenylphosphorane[41] in 25 mL of methylene chloride was heated at reflux for 6 h. The solvent was removed under reduced pressure and the resulting residue was chromatographed on a 1 × 30 cm Florosil column using a 40% ether–pentane mixture as the eluent. The major fraction isolated contained 300 mg (68%) of an orange oil which was identified as *trans*-methyl 2′-(2*H*-azirin-3-yl)-2-biphenylacrylate (**23**) on the basis of the following spectral data: IR (neat) 5.74, 6.08, 6.21, 6.93, 7.54, 7.81, 8.29, 8.47, 10.13, and 13.00 μm; UV (cyclohexane) 272 nm (ε 16 500); NMR (100 MHz, $CDCl_3$) τ 8.68 (s, 2 H), 6.33 (s, 3 H), 3.61 (d, 1 H, J = 16.0 Hz), 2.14–2.76 (m, 8 H), and 1.81–1.96 (m, 1 H); mass spectrum m/e 277 (M^+), 246, 245, 244, 219, 218, 217, 204, 203, 191, 190, 179, 178 (base), 177, 176, 165, and 142.

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.16; H, 5.48; N, 5.20.

Irradiation of *trans*-Methyl 2′-(2*H*-Azarin-3-yl)-2-biphenylacrylate (23) in Benzene. A 390-mg sample of *trans*-methyl 2′-(2*H*-azirin-3-yl)-2-biphenylacrylate (**23**) in 400 mL of distilled benzene was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Corex filter sleeve for 30 min. The solvent was removed under reduced pressure, and the crude residue was chromatographed on a 2 × 30 cm Florosil column using a 1:1 pentane–ether mixture as the eluent. The major component isolated was a white solid, 165 mg (43%), which was recrystallized from acetone–pentane to give methyl 1*H*-dibenz[*e*,*g*]indole-3-carboxylate (**25**) as a white crystalline solid: mp 219–220 °C; IR (KBr) 2.99, 5.92, 6.18, 6.50, 6.91, 7.28, 7.72, 8.35, 8.50, 8.81, 8.98, 9.22, 9.89, 10.49, 10.70, 13.34 and 13.88 μm; UV (cyclohexane) 254 (ε 27 400), 261 (ε 38 000), 286 (ε 5640), 293 (ε 5660), and 306 nm (ε 3430); NMR (60 MHz, acetone-d_6) τ 6.12 (s, 3 H), 2.35–2.60 (m, 5 H), 2.02 (s, 1 H), 1.68–1.88 (m, 1 H), 1.23–1.48 (m, 2 H), and 0.18–0.40 (m, 1 H); mass spectrum m/e 276, 275 (M^+ and base), 245, 244, 214, 189, 137.5 (M^{2+}), 122, 107.5, and 94.5.

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.37; H, 4.97; N, 5.08.

Irradiation of 2′-(2*H*-Azirin-3-yl)-2′-biphenylcarboxaldehyde (20) in Benzene. A 130-mg sample of azirinyl aldehyde **20** in 150 mL of distilled benzene was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Corex filter sleeve for 30 min. The solvent was removed under reduced pressure, and the crude residue was subjected to preparative thick-layer chromatography using a 1:1 pentane–ether mixture as the eluent. The major band isolated contained 54 mg (41%) of an orange solid which was recrystallized from cyclohexane to give phenanthro[9,10-*d*]oxazole (**24**), mp 145–147 °C. The structure of the photoproduct was assigned on the basis of its elemental analysis and spectral properties: IR (KBr) 6.14, 6.65, 8.08, 8.53, 9.28, 9.61, 10.38, 11.60, 13.40 and 13.87 μm; UV (cyclohexane) 252 (ε 55 300), 277 (ε 11 500), 287 (ε 8030), and 300 nm (10 300); NMR (60 MHz, $CDCl_3$) τ 1.88–2.56 (m, 5 H), 1.85 (s, 1 H), and 1.20–1.61 (m, 2 H); mass spectrum m/e 220, 219 (M^+ and base), 191, 190, 164, 163, 109.5 (M^{2+}) and 82.

Anal. Calcd for $C_{15}H_9NO$: C, 82.17; H, 4.14; N, 6.39. Found: C, 82.15; H, 4.24; N, 6.17.

The structure of the photoproduct (**24**) was unambiguously established by comparison with an authentic sample which was prepared by the iodine-catalyzed photooxidation of 4,5-diphenyloxazole.[32]

Preparation of *N*-(*p*-Nitrobenzyl)-2′-vinyl-2-biphenylcarboximidoyl Chloride (26). A solution containing 2.24 g of 2′-vinyl-2-biphenylcarboxylic acid,[42] 2.4 g of thionyl chloride, and 3 drops of pyridine in 100 mL of benzene was heated at 70 °C for 1 h. The solvent and excess thionyl chloride were removed under reduced pressure to leave behind 2.30 g (95%) of 2′-vinyl-2-biphenylcarboxylic acid chloride as a pale-yellow oil: IR (neat) 5.59, 6.26, 6.39, 6.82, 8.37, 8.91, 10.05, 11.54, and 12.94 μm. The crude product was used immediately in the next step. To a solution containing the above acid chloride in 50 mL of ether at 0 °C was added 1.67 g of *p*-nitrobenzylamine[43] in 30 mL of ether. After the addition was complete, the mixture was allowed to warm to room temperature and then 20 mL of a 1 M sodium hydroxide solution was added. After stirring at 25 °C for 30 min, 20 mL of water was added and the ethereal layer was separated from the basic aqueous layer. The ether extracts were washed with a 5% aqueous hydrochloric acid solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 2.90 g (81%) of *N*-(p-nitrobenzyl)-2′-vinyl-2-biphenylcarboxamide as a white solid: mp 111–112 °C; IR (KBr) 3.09, 6.15, 6.65, 7.45, 7.69, 7.79, 8.67, 9.09, 9.85, 10.19, 10.98, 11.73, 12.72, 13.19, and 14.40 μm; NMR (60 MHz, $CDCl_3$) τ 5.78 (d, 2 H, J = 6.0 Hz), 4.97 (dd, 1 H, J = 10.0 and 1.5 Hz), 4.53 (dd, 1 H, J = 18.0 and 1.5 Hz), 3.31–3.90 (m, 2 H), 3.10 (d, 2 H, J = 8.0 Hz), 2.20–3.05 (m, 8 H), and 2.11 (d, 2 H, J = 8.0 Hz); mass spectrum m/e 358 (M^+), 328, 219, 208, 207, 180, 179 (base), 178, 165, 152, 151, 149, 121, 120, and 106.

Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.56; H, 4.93; N, 7.65.

To a solution containing 250 mg of *N*-(*p*-nitrobenzyl)-2′-vinyl-2-biphenylcarboxamide in 5 mL of dry benzene under a nitrogen atmosphere was added 166 mg of phosphorus pentachloride in 5 mL of dry benzene. The mixture was heated at 60 °C until the evolution of hydrogen chloride gas had ceased. The solvent and phosphoryl chloride were removed under reduced pressure leaving behind a pale-yellow oil which was identified as *N*-(*p*-nitrobenzyl)-2′-biphenylcarboximidoyl chloride (**26**) from the following spectral properties: IR (neat) 3.26, 5.94, 6.20, 6.56, 7.41, 8.97, 9.78, 11.56, and 12.99 μm; NMR (60 MHz, $CDCl_3$) τ 5.40 (s, 2 H), 4.96 (dd, 1 H, J = 10.0 and 1.5 Hz), 4.50 (dd, 1 H, J = 18.0 and 1.5 Hz), 3.51 (dd, 1 H, J = 18.0 and 10.0 Hz), 3.09 (d, 2 H, J = 8.0 Hz), 2.16–2.93 (m, 8 H), and 2.08 (d, 2 H, J = 8.0 Hz). The unstable imidoyl chloride was used immediately for the next step.

Reaction of *N*-(*p*-Nitrobenzyl)-2′-biphenylcarboximidoyl Chloride (26) with Triethylamine. To a solution containing 260 mg of the previously prepared imidoyl chloride in 5 mL of dry benzene at 5 °C under a nitrogen atmosphere was added 140 mg of freshly distilled triethylamine. The color of the solution turned yellow-green immediately and then began to turn orange as it slowly warmed to room temperature. After stirring at 25 ° C for 20 h, the solution was passed through a 2 × 30 cm Florosil column using benzene as the eluent. The major component isolated contained 70 mg (30%) of an orange-red solid: mp 167–168 °C, whose structure was assigned as 2,3-dihydro-2-(*p*-nitrophenyl)-1*H*-phenanthro[9,10-*b*]pyrrole (**27**) on the basis of the following spectral data: IR (KBr) 2.98, 6.25, 6.64, 6.95, 7.38, 9.10, 9.81, 10.55, 11.70, 13.33, 1384 μm; UV (cyclohexane) 255 (ε 42 000) and 324 nm (ε 6300); NMR (60 MHz, acetone-d_6) τ 6.83 (dd, 1 H, J = 14.0 and 8.0 Hz), 6.00 (dd, 1 H, J = 14.0 and 10.0 Hz), 4.58 (dd, 1 H, J = 10.0 and 8.0 Hz), 3.87 (br s, 1 H), 1.78–2.76 (m, 10 H), and 1.22–1.77 (m, 2 H); mass spectrum m/e 340 (M^+), 310, 205, 204, 180, 179 (base), 178, 154, 149, 105, and 77.

Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.50; H, 4.68; N, 7.84.

Photoaddition of 3,3′-(2,2′-Biphenylylene)bis[2*H*-azirine] (18) with Dimethyl Acetylenedicarboxylate. A 100-mg sample of **18**[27] in 150 mL of benzene which contained 61 mg of dimethyl acetylenedicarboxylate was irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter sleeve for 30 min. Removal of the solvent left a dark residue which was subjected to thick-layer chromatography using a 1:1 ether–hexane mixture as the eluent. The major component isolated (43 mg) was a crystalline solid, mp 169–170 °C, whose structure was assigned as dimethyl 2*H*,4*H*-phenanthro[9,10-*d*]pyrrolo[1,2-c]imidazole-5,6-dicarboxylate (**28**) on the basis of the following data: IR (KBr) 5.84, 6.04, 6.94, 7.03, 7.57, 7.94, 8.74, 9.30, 10.42, 13.04, 13.18, and 13.66; UV (methanol) 242 nm (ε 39 250); NMR ($CDCl_3$, 60 MHz) τ 6.88 (s, 3 H), 6.32 (s, 3 H), 6.10 (d, 1 H, J = 17.0 Hz), 5.56 (d, 1 H; J = 17.0 Hz), 5.30 (d, 1 H, J = 14.0 Hz), 4.36 (d, 1 H, J = 14.0 Hz), 2.0–2.8 (m, 8 H).

Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.42; H, 4.78; N, 7.27.

Photoaddition of 3,3′-(2,2′-Biphenylylene)bis[2*H*-azirine] (18) with Dimethyl Fumarate. A 100-mg sample of 18 in 150 mL of benzene which contained 62 mg of dimethyl fumarate was irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter sleeve for 30 min. Removal of the solvent left a dark oil which was subjected to thick-layer chromatography using a 15% methanol–benzene mixture as the eluent. The major fraction isolated from the thick-layer plate (81 mg) was a white crystalline solid, mp 132–133 °C, whose structure was assigned as dimethyl (1*H*-phenanthro[9,10-*d*]imidazol-1-yl-

methyl)succinate (**29**) on the basis of the following data: IR (KBr) 5.80, 6.55, 6.90, 7.25, 7.40, 7.75, 8.20, 8.58, 9.23, 13.14, and 13.76 μm; UV (methanol) 255 nm (ε 97 000); NMR ($CDCl_3$, 100 MHz) τ 7.45 (d, 2 H, J = 6.0 Hz), 6.30–6.60 (m, 1 H), 6.40 (s, 3 H), 6.35 (s, 3 H), 5.30 (dd, 1 H, J = 15.0 and 8.0 Hz), 5.10 (dd, 1 H, J = 15.0 and 8.0 Hz), 2.2–2.4 (m, 4 H), 2.15 (s, 1 H), 1.7–1.8 (m, 1 HO), 1.2–1.4 (m, 3 H); mass spectrum m/e 376 (M^+), 232, 219, 187, 186, and 169.

Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.20; H, 5.70; N, 7.13.

The structure of this photoproduct was further verified by comparison with an independently synthesized sample. To a solution containing 220 mg of 4,5-diphenylimidazole in 20 mL of benzene was added 35 mg of sodium hydride. The mixture was allowed to stir at room temperature for 1 h and then 158 mg of dimethyl itaconate in 5 mL of benzene was added. After stirring at 25 °C for 9 h, the excess sodium hydride was destroyed by the addition of water. The organic layer was extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting yellow residue was subjected to silica gel chromatography using a 1:1 ether–hexane mixture as the eluent. The major fraction contained 55 mg of dimethyl (4,5-diphenylimidazol-1-ylmethyl)succinate (**35**) as a clear oil: NMR ($CDCl_3$, 100 MHz) τ 7.60 (d, 2 H, J = 7.0 Hz), 6.90–7.20 (m, 1 H), 6.44 (s, 3 H), 6.40 (s, 3 H), 6.04 (dd, 1 H, J = 13.0 and 7.0 Hz), 5.72 (dd, 1 H, J = 13.0 and 7.0 Hz), 2.40–2.95 (m, 11 H). A 75-mg sample of **35** in 200 mL of benzene containing 254 mg of iodine was irradiated through Pyrex for 48 h. The excess iodine was destroyed by washing with a 10% sodium thiosulfate solution. After drying the organic layer, the solvent was removed under reduced pressure to give a sample of **29** which was identical in every detail with that obtained from the irradiation of bis(azirine) **18** with dimethyl fumarate.

Photoaddition of 3,3′-(2,2′-Biphenylylene)bis[2*H*-azirine] (18) with Methyl Acrylate. A 100-mg sample of **18** in 150 mL of benzene which contained 5 mL of methyl acrylate was irradiated with a 450-W hanovia lamp equipped with a Pyrex filter sleeve. Removal of the solvent left an orange oil which was subjected to thick-layer chromatography using a 15% methanol–benzene mixture as the eluent. The major band isolated from the thick-layer plate (85%) was a crystalline solid, mp 76–77 °C, whose structure was assigned as methyl (1*H*-phenanthro[9,10-*d*]imidazole-1-yl)butyrate (**30**) on the basis of the following data: IR (KBr) 5.74, 6.54, 7.00, 7.33, 7.85, 8.50, 10.09, 11.70, 12.08, 13.50, and 13.90 μm; UV (methanol) 255 nm (ε 75 000); NMR ($CDCl_3$, 100 MHz) τ 7.80 (m, 4 H), 6.35 (s, 3 H), 5.60 (m, 2 H), 2.4–2.7 (m, 4 H), 2.35 (s, 1 H), 1.3–2.2 (m, 4 H); mass spectrum m/e 318 (M^+), 232, 219, 218, and 178.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80; Found: C, 75.30; H, 6.01; N, 8.49.

Acknowledgment. We gratefully acknowledge the National Science Foundation for financial support. Aid in the purchase of the NMR spectrometer (XL-100) used in this work was provided by the NSF via an equipment grant.

Registry No.—**1**, 16231-67-7; **2**, 64024-87-9; **3**, 63626-12-0; **5**, 64024-90-4; **6**, 64024-91-5; **7**, 64024-93-7; **13**, 64024-95-9; **14**, 63375-55-3; **18**, 63626-10-8; **19**, 64024-97-1; **20**, 64024-96-0; **21**, 235-96-1; **22**, 26093-30-1; **23**, 64024-98-2; **24**, 64024-99-3; **25**, 64025-00-9; **26**, 64025-01-0; **27**, 64025-02-1; **28**, 64024-84-6; **29**, 64024-85-7; **30**, 64024-86-8; **35**, 64024-88-0; 2′-vinyl-2-biphenylmethanol, 64024-89-1; *N*-phenylhydroxylamine, 100-65-2; sodium azide, 26628-22-8; carbomethoxytriphenylphosphosphorane, 2605-67-6; 2′-vinyl-2-biphenylcarboxylic acid, 64024-92-6; thionyl chloride, 7719-09-7; *N*-(*p*-nitrobenzyl-2′-vinyl-2-biphenylcarboxamide, 64024-94-8; dimethyl acetylenedicarboxylate, 762-42-5; dimethyl fumarate, 624-49-7; 4,5-diphenylimidazole, 668-94-0; dimethyl itaconate, 617-52-7; methyl acrylate, 96-33-3; methyltriphenyl phosphonium bromide, 1779-49-3.

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Reactivity of 1,3-Dipoles in Aqueous Solution. 2. Stereospecific Reactions of Benzonitrile Oxides with Oxygen, Carbon, and Nitrogen Nucleophiles

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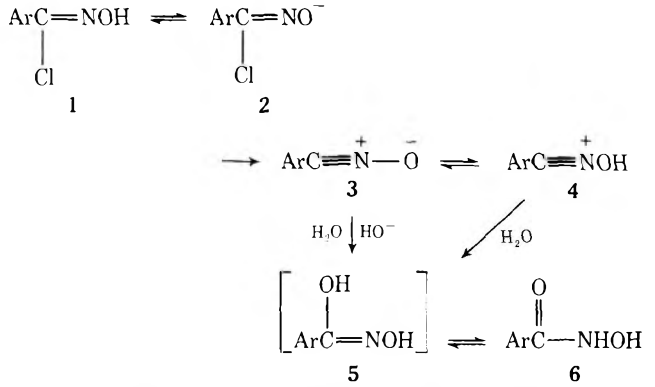
Received May 31, 1977

The reactivities of substituted benzonitrile oxides **3** (generated in situ from the corresponding chlorides **1**) have been examined in aqueous solution; simple second-order reactions were observed with nucleophiles and with acrylonitrile. Substituent variation in Ar gave the following Hammett ρ values: +0.57 (H_2O), +0.80 (HO^-), and +0.75 ($CH_3CO_2^-$). With alkoxide ions as nucleophiles, only the (*Z*)-*O*-alkylhydroxamic acid **10** is formed. Evidence is also presented that only *Z* isomers (in which the entering nucleophile at carbon and forming lone pair on nitrogen are trans) are also formed with the nucleophiles $CH_3CO_2^-$, N_3^-, Cl^-, and carbanions. Cycloaddition of acrylonitrile to **3** is characterized by a similar low sensitivity to substituents in the benzonitrile oxide (ρ = +0.36). Both cycloaddition of benzonitrile oxides to alkenes and reaction of nucleophiles at carbon are therefore characterized by similar transition states, and the key role of carbon-nucleophile bond formation in determining stereospecificity is discussed.

In the previous paper in this series,[1] we reported on the reactivity of benzonitrile oxides with primary and secondary amines and the stereospecific formation of (*Z*)-amidoximes. We have now extended this to a kinetic study involving oxygen nucleophiles (HO^-, H_2O, $CH_3CO_2^-$) and report on the unique stereochemistry both of these reactions and the reaction of nitrile oxides with other nucleophiles. Since nucleophilic attack at the carbon of the nitrile oxide is a possible model for the first step in the alternative two-step mechanism of 1,3-dipolar cycloaddition to alkenes, the relevance of the observed stereospecificity of the first step is also considered.

Results and Discussion

Neutral Hydrolysis. The required benzonitrile oxides **3** were prepared in aqueous solution by rapid dehydrohalogenation of the corresponding hydroxamoyl chlorides.[1] The conversion of **1** to **3** is base catalyzed and rapid ($t_{1/2}$ < 1 s) at pH >4 in water at 25 °C. The subsequent reaction of **3** with water is surprisingly slow and could be conveniently measured. At pH <8, the reaction with **3** (Ar = *p*-$MeOC_6H_4$) is independent of pH, consistent with H_2O as the nucleophile in this region.



Buffer catalysis (by acetate ion) was noted in the presence of acetate buffers (see below); the rates of reaction of substituted benzonitrile oxides with water were therefore measured (at 61 °C) by extrapolation of k_{obsd} vs. buffer concentration plots to zero buffer concentration. The results (at pH 4.65) are summarized in Table I. The low sensitivity of the reaction to substituents in the nitrile oxide is obvious from the Hammett ρ value of +0.57 (r = 0.998) calculated from these data.

The products of hydrolysis under neutral conditions are the corresponding benzohydroxamic acids **6** (which were also prepared by independent synthesis from the ethyl benzoate and hydroxylamine[2]). Under the conditions used to study the kinetics, no detectable further hydrolysis of the benzohydroxamic acids occurs (although it is well established that in concentrated acid or base **6** hydrolyse to benzoic acids and hydroxylamine).[3] The formation of **6** contrasts with previous reports of complex products,[4,5] although Edwards and Tremaine[6] also observed the quantitative formation of benzohydroxamic acids **6** on hydrolysis of chlorides **1** under mild conditions (aqueous sodium bicarbonate).

Base-Catalyzed Hydrolysis. The reaction of **3** with hydroxide ion was also examined; the products formed were the corresponding benzohydroxamic acids **6**. The rate of reaction was proportional to [HO^-] over a wide range (Table II). Again electron-withdrawing substituents enhanced reactivity to a small extent; the rate constants for reaction with HO^- at 25 °C at pH 11.15 are summarized in Table III. The Hammett ρ value calculated from these data is +0.80 (r = 0.998).

Acid-Catalyzed Hydrolysis. Since the dehydrohalogenation of **1** occurs at a rate comparable to that of acid-catalyzed hydrolysis of **3** at low pH, the latter reaction was examined using the following sequence. The chloride (**1**, Ar = *p*-ClC_6H_4) was added to water (μ = 1.0, $NaClO_4$, 25 °C) at pH ca. 4. The solution was then acidified to the desired pH with concentrated perchloric acid.

Over the pH range 1.0 to 0, the logarithm of the rate of hydrolysis of **3** was inversely proportional to pH (k_{obsd} = 2.4 × 10^{-2} s^{-1} at pH 0). The observation of acid catalysis is interesting, since it implies a mechanism involving rate-determining attack by water on the nitrilium ion **4**; this is the first demonstration of the existence of this species on a reaction pathway.[7] The dehydrohalogenation of **1** might by analogy with the hydrazonoyl halides system **7** occur via an uncatalyzed pathway (involving **4**); however, in spite of a careful examination no evidence for this was found even in 1.0 M acid (where the dehydrohalogenation of **1** remained base catalyzed). The difficulty of formation of **4** by unimolecular solvolysis of **1** was confirmed when *O*-phenylbenzohydroxamoyl chloride **8** was examined in 7:3 water–dioxane at 60 °C in neutral solution and in the presence of 0.1 M sodium hydroxide. No spectral change was observed over a 24 h period. The difficulty of formation of **9** by this route is explicable in terms of the destabilization of the nitrilium ion by the electronegative phenoxy group.

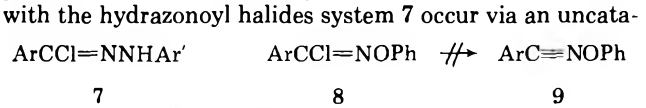


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Table I. Observed Rate Constants for the Hydrolysis of Benzonitrile Oxides (3, Ar = XC_6H_4) at 61 °C in Water at pH 4.65

Substituent X	Registry no.	$10^4 k_{obsd}$, s^{-1} Total acetate buffer concn, M[b] 1×10^{-2}	5×10^{-3}	1×10^{-3}	$10^4 k_{H_2O}$, s^{-1} [a]
p-MeO	15500-73-9	4.68	3.50	2.73	2.25
H	873-67-6	7.90	5.33	3.65	3.10
p-Cl	15500-74-0	12.0	8.45	5.18	4.52
m-Cl	13820-15-0	14.8	10.2	5.83	4.98
m-NO_2	7007-35-4	22.3	15.7	9.17	7.83
p-NO_2	2574-03-0	25.2	16.7	10.8	8.98
o-Cl	49660-38-0	3.65	2.62	1.65	1.45

[a] Obtained by extrapolation to zero buffer concentration. [b] μ = 1.0 ($NaClO_4$).

Table II. Observed Rate Constants for the Hydrolysis of Benzonitrile Oxides (3, Ar = XC_6H_4) at 25 °C in 1:4 Dioxane–Water as a Function of Hydroxide Ion Concentration

[HO^-], M	$10^3 k_{obsd}$, s^{-1} X = *p*-Cl	X = *p*-MeO	X = *p*-NO_2
0.25		120	
0.125		66	
0.062	86.8	33	
0.031	42.1	17	132
0.016	21.4	8.0	64
0.0078	11.1	3.5	27.2
0.0039	5.40		12.0
0.0020	2.60		

Table III. Observed Rate Constants for Hydroxide-Catalyzed Hydrolysis of 3 (Ar = XC_6H_4) in Water at pH 11.15 at 25 °C

Substituent X	λ, nm[a]	$10^3 k_{obsd}$, s^{-1}
p-MeO	270	4.89
H	250	7.37
p-Cl	265	11.8
m-Cl	255	14.4
p-NO_2	310	33.2
m-NO_2	294	40.7

[a] Wavelength used to follow course of reaction.

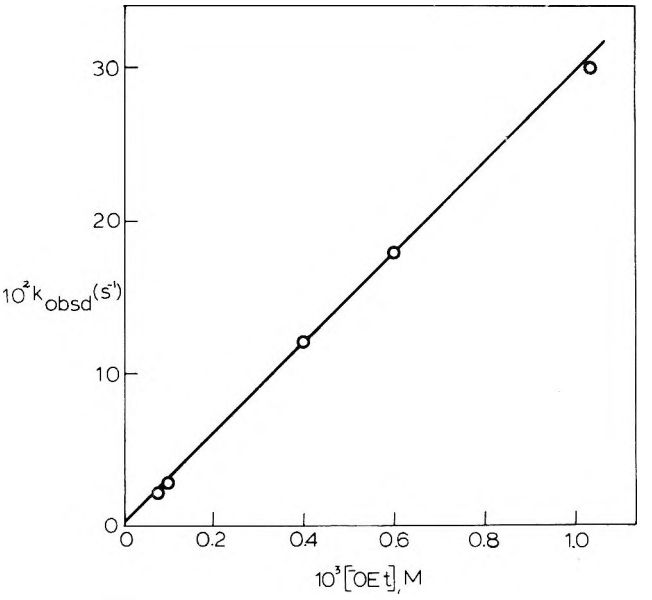
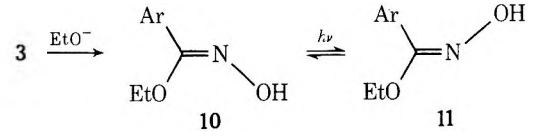


Figure 1. Plot of observed rate (s^{-1}) of reaction of **3** (Ar = *p*-$NO_2C_6H_4$) with sodium ethoxide in ethanol at 25 °C.

Stereochemistry of Addition: (a) Ethoxide Ion. Addition of hydroxide ion to nitrile oxides **3** initially gives **5** which tautomerizes to the more stable benzohydroxamic acid **6**. The intermediates **5** are potentially isolable in two forms which differ in the configuration about the C=N bond; the rapid tautomerism via **6** would ensure equilibration of these isomers. The stereochemistry of the original addition was therefore probed using alkoxide in place of hydroxide.

Preliminary experiments showed (Figure 1) that the rate of reaction of *p*-nitrobenzonitrile oxide (**3**, Ar = *p*-$NO_2C_6H_4$) with sodium ethoxide in ethanol was overall second order, first order in ethoxide ion and the nitrile oxide over a wide concentration range. The product isolated on neutralization of the solution was a single isomer to which we assign the *Z*-configuration **10**. The assignment was based on literature data,[9,10] and on comparison with authentic samples of **10** and **11** (Ar = Ph). The assignment was confirmed by isomerization of **10** (Ar = *p*-$NO_2C_6H_4$) on irradiation at 70 °C for 2 h in benzene to a mixture of **10** and **11**. The NMR spectrum of the *E* isomer **11** showed an upfield shift of 0.25 ppm for the



10 **11**

methylene proton quartet (similar to that observed for **10** and **11**, Ar = Ph). In Me_2SO the =NOH protons gave a sharp NMR signal, that in the *E* form **11** being 0.9-ppm upfield from that in the *Z* isomer **10**. A similar upfield shift was also noted with *Z*/*E* isomer mixtures of amidoximes also measured in Me_2SO.[11]

A single *Z* isomer was also formed on reaction of **3** (Ar = *p*-$NO_2C_6H_4$) with methoxide ion (see Experimental Section).

(b) Acetate. The rates of reaction of *p*-nitrobenzonitrile oxide (**3**, Ar = *p*-$NO_2C_6H_4$) in the presence of different concentrations of acetate buffers were measured in water at pH 4.65 at 50 °C (Figure 2, see also Table I). Clearly, acetate ion is the reactive species since no significant catalysis is observed at pH 3 where acetate is converted almost entirely to its conjugate acid. From these data, a second-order rate constant for the reaction of acetate ion with the nitrile oxide of 0.30 M^{-1} s^{-1} was calculated. Examination of other substituted benzonitrile oxides gave (Figure 3) a ρ value of +0.75 (r = 0.996), very similar to that reported above for the reaction of the other negatively charged nucleophile, HO^-.

Repetitive scans of the ultraviolet spectrum during the reaction of **3** with acetate ion showed tight isosbestic points, indicating the absence of relatively long-lived intermediates during reaction. The product of reaction was not the *O'*-acetyl benzohydroxamic acid **12** as expected by analogy with the reaction product from other nucleophiles, but the isomeric *O*-acetylbenzohydroxamic acid **13**. The latter was prepared independently by acetylation of *p*-nitrobenzohydroxamic

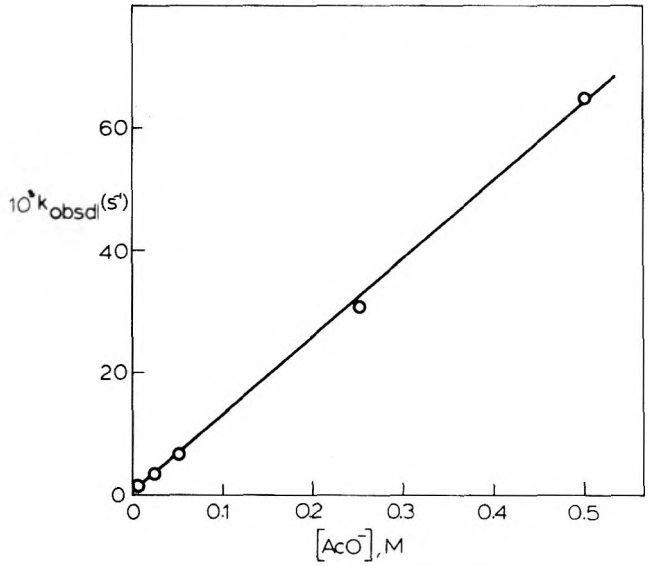
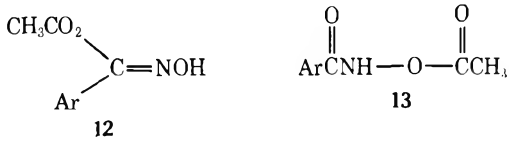
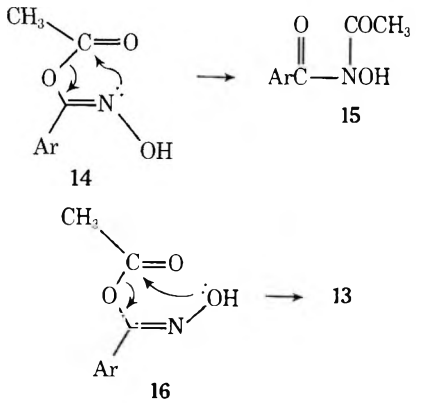


Figure 2. Plot of observed rate constants (s^{-1}) for the reaction of **3** (Ar = p-$NO_2C_6H_4$) with acetate ion in water at pH 4.6 in H_2O at 50 °C.

acid, and its structure, although controversial, follows from the work of Just and Dahl.[12-15]



The quantitative formation of **13** can be related as follows to the configuration of the original product **12** formed on reaction of **3** with acetate ion. Thus, the E-isomer **14**, if formed, would either be isolated as such (without rearrangement) or as the isomeric N-acyl material **15**. This follows from recent work[16] on the corresponding O-alkyl derivatives of **14**, which are relatively stable at ambient temperatures but undergo isomerization to O-alkylated **15** at ca. 70 °C. However, if the initial products are of the Z-configuration **16** then rapid O′ → O acyl group migration via a five-membered ring gives the observed O-acyl products **13**. Since oximes undergo extremely slow EZ isomerization, **14** and **16** are not interconvertible; therefore, the quantitative isolation of **13** provides good evidence that **16** was initially formed.



(c) Azide Ion. Open-chain hydroxamoyl azides **17** are formed on reaction of nitrile oxides **3** with azide ion, although in general imidoyl azides are unstable relative to cyclization to isomeric tetrazoles.[19] Recent theoretical studies have emphasized the importance of the cis arrangement of the azido group and the long pair on the imine nitrogen.[20] We therefore conclude that the imidoyl azides have the Z-configuration **17**.

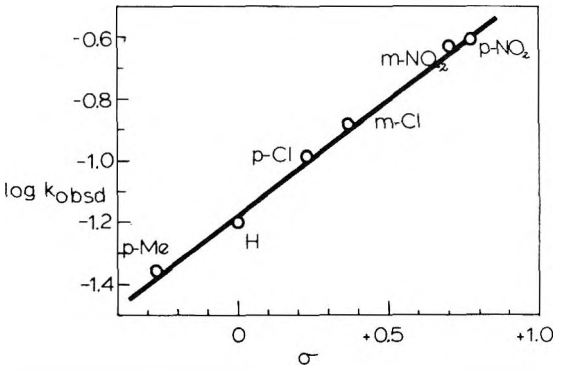
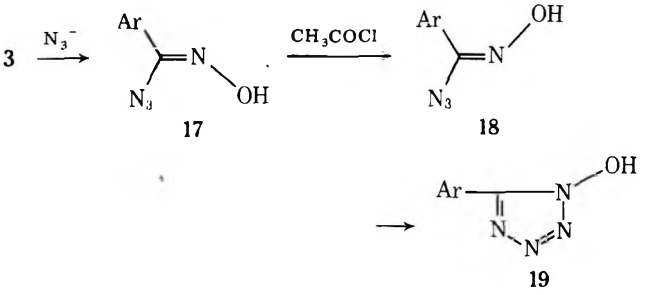
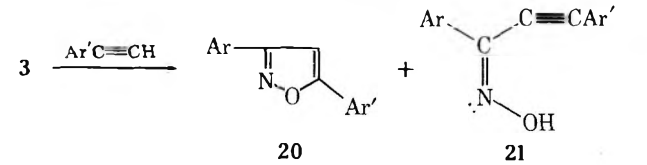


Figure 3. Plot of log k_2 [k_2 is the second-order rate constant ($M^{-1}\,s^{-1}$) for the reaction of acetate ion with nitrile oxides (**3**, Ar = XC_6H_4)] vs. Hammett σ values (at 50 °C, μ = 1.0, $NaClO_4$); ρ = +0.75.

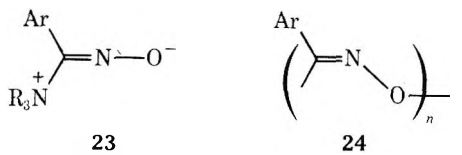
Interestingly, it has recently been shown[21] that treatment of the azides **17** with acetyl chloride at reflux catalyzes the cyclization of **18** to the isomeric N-hydroxytetrazole **19**. These are conditions known to promote EZ equilibration of oximes;[22] presumably, the E isomer **18** formed by this route spontaneously cyclizes to the more stable **19**.



(d) Carbanions. Reaction of nitrile oxides with arylacetylenes gives in addition to the normal cycloadduct **20** the open-chain acetylenic oxime **21**.[23-25] Higher yields of the oxime are obtained when the acetylide ion is used.[26] The configuration of the oxime **21** formed has not been unequivocally established but it is most likely Z (as shown), since (a) cyclization of the oxime to **20** is facile and quantitative in base[25] (conditions unlikely to promote EZ isomerization of oximes[27]) and (b) reduction of the acetylene followed by Beckmann rearrangement also indicates the Z configuration for **21**.[24]



(e) Polymerization. It has been shown recently[28] that polymerization of nitrile oxides **3** is catalyzed by tertiary amines. The proposed mechanism involves the equilibrium formation of a small concentration of the zwitterion **23** which



then acts as a nucleophile toward further nitrile oxide, ultimately giving polymers and macrocycles of general formula **24**. Crystallographic studies[29] have shown that in the macrocycle **24** (n = 8) all of the C=N linkages have the Z configuration, implying stereospecific reaction of **23** with **3**.

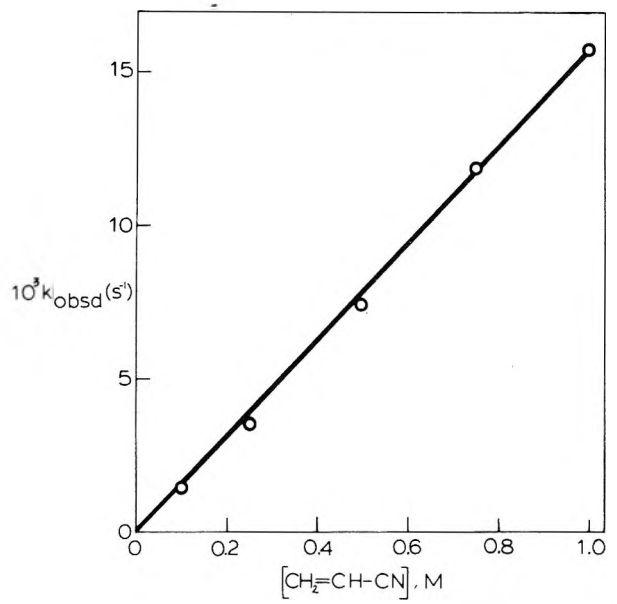
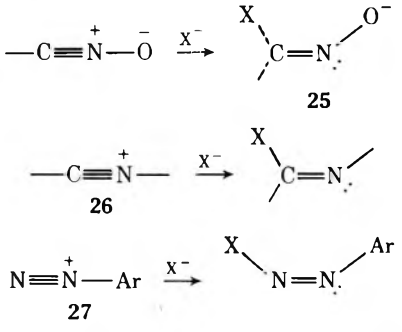


Figure 4. Observed rate constants (in s^{-1}) for the reaction of **3** (Ar = p-$NO_2C_6H_4$) at 25 °C as a function of added acrylonitrile.

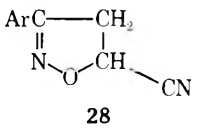
(f) Chloride Ion. When the nitrile oxide **3** is treated with concentrated hydrochloric acid, the equilibrium is reversed and the hydroxamoyl chloride **1** is re-formed.[30] The configuration of **1** formed by this route has been established (by x-ray crystallography) as Z.[31] However, in this case the corresponding E isomer has not been reported, so the assignment of (Z)-**1** as the kinetic product is not unequivocal [e.g., (E)-**1** may be formed which rapidly isomerizes to a thermodynamically more stable (Z)-**1**].

In summary, in each case in which an unequivocal assignment of structure can be made, it is shown that on reaction of the 1,3-dipole **3** with nucleophiles only the product with the Z configuration is formed. In several other cases there is good evidence that the same stereospecificity exists. In the products formed, the entering nucleophile and the forming lone pair on the adjacent nitrogen are mutually *trans*-**25**, and this appears to be the critical factor which determines the stereo-



chemistry of the product. The nitrile oxides are therefore directly analogous to nitrilium ions[32] **26** and aryl diazonium ions[33] **27** which show just the same type of stereospecificity.

Cycloaddition. In order to compare the charge distributions in the transition states for nucleophilic attack on the 1,3-dipole with 1,3-dipolar cycloaddition, the reaction with acrylonitrile in aqueous solution was also examined. The rate of cycloaddition is proportional to acrylonitrile concentration (see Figure 4) and the formation of **28** under these conditions



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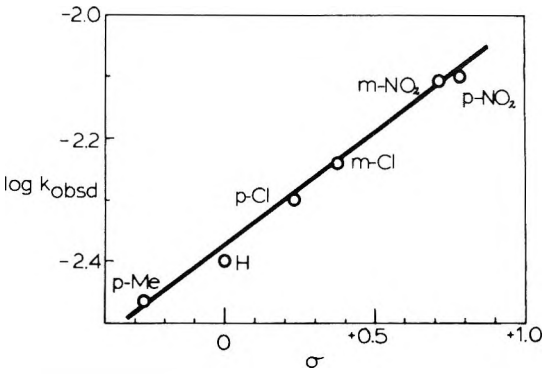


Figure 5. Plot of log k_{obsd} [k_{obsd} is the observed rate of reaction of **3** (Ar = XC_6H_4) with acrylonitrile (0.25 M) in water at 25 °C] vs. Hammett σ values; ρ = +0.36.

Table IV. Second-Order Rate Constants for the Reaction of 3 (Ar = p-$NO_2C_6H_4$) (a) in Water and (b) in 1:1 Dioxane–Water at 25 °C

Dipolarophile	(a) 10^3k, $M^{-1}\,s^{-1}$	(b) $10^3\,k$, $M^{-1}\,s^{-1}$
Ethyl acrylate	145	75.6
Dimethyl fumarate		58.4
Methyl methacrylate		56.4
Ethyl propiolate		26.8
Acrylonitrile	29.3	
Dimethyl maleate	5.0	3.48
Methyl crotonate		2.50

[a] μ = 1.0, $NaClO_4$; pH maintained at 4.65 by 5 × 10^{-3} M acetate buffer; the solubility of the other dipolarophiles was too low to permit measurements in H_2O. [b] μ = 0.25, $NaClO_4$; pH = 4.0 (2 × 10^{-3} M acetate).

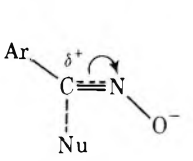
was confirmed by TLC and actual isolation using an authentic sample.

The effect of substituents in the 1,3-dipole was investigated in water at 25 °C using 0.25 M acrylonitrile. A plot of log k_{obsd} vs. Hammett σ values gave a ρ value of +0.36 (r = 0.995) (see Figure 5). The small positive ρ value obtained in aqueous solution is consistent with previous values of +0.79 (styrene as dipolarophile in carbon tetrachloride)[34] and +0.60 (phenylacetylene)[35] reported for substituents in nitrile oxides.

The order of reactivity of various 1,3-dipolarophiles in aqueous solution and in 1:1 dioxane–water (Table IV) is the same as that observed by Huisgen from competitive experiments in diethyl ether,[36] although the spread of reactivity is slightly less (e.g., $k_{ethyl\ acrylate}/k_{dimethyl\ maleate}$ is 38 in diethyl ether).[36] These results extend and confirm the remarkable insensitivity to solvent shown by the rates of cycloaddition even in solvents as disparate as diethyl ether and water.

The similarity in the magnitude and sign of the ρ values obtained for reaction of **3** with water, hydroxide ion, acetate ion, and with amines[1] to that for cycloaddition to an alkene measured under the same conditions indicates like charge distributions in the transition states for both reactions. There is convincing evidence[37] that cycloaddition to **3** occurs via an early transition state, which is reached while there is still little C–C or C–O bond formation (the low solvent effect observed on the rate of cycloaddition confirms this). Nucleophilic attack at the carbon of **3** is also characterized by an early transition state with little C–nucleophile bond formation.[1] However, in spite of the early transition state in the latter reaction, the stereochemistry of the kinetic product implies that the interaction of the initially linear nitrile oxide **3** with the nucleophile in the transition state is sufficient to bend the dipole

so that the oxygen is adjacent to the incoming nucleophile **29**.



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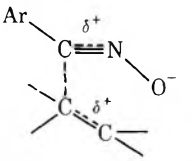

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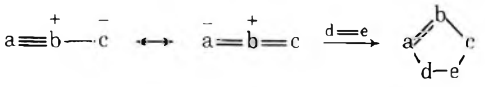
It is interesting that recent ab initio molecular-orbital studies of the reaction pathway for the addition of simple nitrile oxides to alkenes and alkynes show[38] that the only significant geometry change in passing from reactants to transition state is a marked bending of the $-C{\equiv}N^{+}-O^{-}$ skeleton (**30**), the C–C and C–O bonds remaining long. This bending of the C–N–O group from 180° to 144° in the transition state (all the atoms are coplanar) requires the major portion (55 kJ mol^{-1} relative to 89 kJ mol^{-1}) of the energy required to bring the reactants to the transition state. Once this bending of the 1,3-dipole has occurred, the alkene carbon and nitrile oxide oxygen are correctly placed (**30**) to allow ring closure to occur in a rapid subsequent step. Clearly then the factors which determine the stereospecificity of reactions of nucleophiles with nitrile oxides (and also with nitrilium ions and diazonium ions) can also be invoked in cycloadditions to alkenes without implying any C–O bond formation in the transition state **30**.

These observations may have wide generality for 1,3-dipolar cycloadditions, since in each of the propargyl–allenyl type 1,3-dipoles **31** (which like **3** are linear) a pair of electrons originally involved in the π system of the 1,3-dipole becomes localized on the central atom of the original 1,3-dipole (b) in the product **32**. The most important factor in the transition state for the formation of **32** may be the nucleophilic character of the alkene (d=e), the small amount of a–d bond formation being sufficient to induce the required bending of the 1,3-dipole.



31a **31b** **32**

Experimental Section

General. Melting points were determined on an electrothermal apparatus and are uncorrected. uv spectra for product analysis were run on a Unicam SP-800 B spectrophotometer. A Perkin Elmer Model R20A was used for NMR spectra. All inorganic salts were Analar grade. Aqueous sodium hydroxide solutions were made up from Volucon (M & B) standard ampules and the perchloric acid from 60–62% Analar perchloric acid. Dioxane was Analar grade and was used without further purification.

Substrates. All hydroxamoyl chlorides were prepared as previously described.[1] The following were made by standard literature methods: *O*-phenylbenzohydroxamoyl chloride (**8**, Ar = Ph), mp 35–36 °C (lit.[39] 35–36 °C); benzohydroxamic acid (**6**, Ar = Ph), mp 125–128 °C (lit.[2] 125–128 °C); *p*-nitrobenzohydroxamic acid (**6**, Ar = *p*-$NO_2C_6H_4$), mp 182–184 °C (lit.[40] 177 °C, 186 °C dec); *O*-acetylbenzohydroxamic acid (**13**, Ar = Ph), mp 123 °C (lit.[12] 125 °C).

Product Analysis. (*Z*)-Ethyl *p*-Nitrobenzohydroximate (10, Ar = *p*-$NO_2C_6H_4$). Sodium ethoxide (5 equiv) was added to *p*-nitrobenzchydroxamoyl chloride (1 equiv) in ethanol and stirred for 10 min. The solution was diluted fivefold with water and neutralized by bubbling carbon dioxide through the solution. The mixture was extracted with chloroform, and the combined extracts were dried over sodium sulfate and evaporated to leave a light yellow solid which, on recrystallization from cyclohexane, had mp 94–95 °C (lit.[9] 95 °C): NMR (Me_2SO-d_6) δ 1.36 (t, 3, J = 7 Hz, OCH_2CH_3), 4.46 (q, 2, J = 7 Hz, OCH_2CH_3), 7.9–8.5 (m, 4, aromatic H), 11.21 (s, 1, OH). Irradiation of a sample of **10** (Ar = *p*-$NO_2C_6H_4$) in dry benzene for 2 h at 70 °C with a Hanovia 100-W medium-pressure lamp in a quartz apparatus gave a 50:50 mixture of *ZE* isomers. For **11** (Ar = *p*-$NO_2C_6H_4$): NMR (Me_2SO-d_6) δ 1.36 (t, 3, J = 7 Hz, OCH_2CH_3), 4.22 (q, J = 7 Hz), 4.46 (q, J = 7 Hz) (*Z*, OCH_2CH_3), 7.9–8.5 (m, 4, aromatic H), 10.44, 11.21 (s, 1, OH).

(*Z*)-Methyl *p*-Nitrobenzohydroximate. Sodium methoxide (5 equiv) was added to *p*-nitrobenzohydroxamoyl chloride (1 equiv) in methanol and stirred for 10 min. The solution was diluted fivefold with water and neutralized by bubbling carbon dioxide through the solution. The mixture was extracted with chloroform and the combined extracts were dried over sodium sulfate and evaporated to leave a light yellow solid which, on recrystallization from cyclohexane, had mp 128–129 °C: NMR (Me_2SO-d_6) δ 4.09 (s, 3, OCH_3), 7.9–8.6 (m, 4, aromatic H), 11.18 (s, 1, OH). Anal. Calcd for $C_8H_8N_2O_4$: C, 4 .98; H, 4.11; N, 14.28. Found: C, 48.98; H, 4.03; N, 14.37. Irradiation as above gave a 40:60 mixture of *ZE* isomers: NMR (Me_2SO-d_6) δ 3.84 (s), 4.08 (s) (3, OCH_3), 7.9–8.6 (m, 4, aromatic H), 10.51, 11.18 (s, 1, OH).

Reaction of *p*-Nitrobenzohydroxamoyl Chloride with Acrylontrile in 50% Dioxane–Water. Sodium acetate (2 equiv) and perchloric acid (1 equiv) were added to 50% dioxane–water containing acrylonitrile (10 equiv). To this solution was added *p*-nitrobenzohydroxamoyl chloride (0.1 equiv), and the solution was stirred at room temperature for 24 h. It was then extracted with ether (three times) and the combined ether extracts were extracted in turn with water (two times). The ether extract was then dried with sodium sulfate and evaporated to dryness under reduced pressure at room temperature. TLC indicated that the yellow solid which remained was principally the oxadiazole **28** together with a small amount of unreacted starting material. Preparative TLC (silica gel with ether) gave pure 3-*p*-nitrophenyl-5-cyano-1,2,4-oxadiazole (**28**, Ar = *p*-$NO_2C_6H_4$) (79%), mp 157–158 °C. Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.29; H, 3.23; N, 19.35. Found: C, 55.01; H, 3.25; N, 19.20.

Kinetic Method. All rate data were measured on a Unicam SP-800 B spectrophotometer fitted with a scale expansion accessory at previously described wavelengths.[1] Substrates were made up 10^{-2} M in dioxane (Analar). pHs were measured using a Radiometer Model PHM 26 pH meter fitted with a Metrohm EA-125U glass electrode. The techniques used for following the kinetics have already been fully described.[41]

The products formed during a kinetic experiment were determined spectrophotometrically using authentic samples and confirmed using TLC analysis. When the product had a pK_a in the accessible region (e.g., the benzohydroxamic acids, **6**) as an addition, check the pK_a was determined in situ using the combined pH–stat spectrophotometer. The difference in absorbance between the acidic and basic forms of the product was also used to show that the formation of the hydroxamic acid was quantitative.

Attempted Reaction of *O*-Phenylbenzohydroxamoyl Chloride (8). The chloride was dissolved (10^{-4} M) in 3:7 dioxane–water at neutral pH and maintained (a) at neutral pH for 1 week at 25 °C and (b) for 24 h at 60 °C in the presence of 0.1 M sodium hydroxide. In neither case did a detectable reaction occur. Since the starting chloride **8** and the expected product *O*-phenylbenzohydroxamic acid have similar UV spectra in basic solution [λ_{max} 282 nm (ϵ 7800), 268 nm (ϵ 8500), and 272 nm (ϵ 7600), respectively], the solution was acidified at the end of the reaction period. The spectrum of *O*-phenylbenzohydroximate changed under these conditions [λ_{max} 272 nm (ϵ 1900), 268 nm (ϵ 2200)], whereas that of the chloride **8** was unaltered; any conversion to the hydroxamic acid would therefore have been detectable. The chloride **8**, mp 35–36 °C, (lit.[42] 35–36 °C), was also recovered unchanged when attempted reaction was carried out on a preparative scale.

Acknowledgment. We are grateful to the Department of Education for a State Maintenance Allowance for Research (to K.J.D. and P.L.Q.) and to Dr. J. E. Johnson for samples of **10** and **11** (Ar = Ph).

Registry No.—**1** (Ar = *p*-$NO_2C_6H_4$), 1011-84-3; **10** (Ar = *p*-$NO_2C_6H_4$), 7340-18-3; **11** (Ar = *p*-$no_2C_6H_4$), 64011-07-0; **28**, 64011-09-2; (*Z*)-methyl-*p*-nitrobenzohydroximate, 64011-08-1; (*E*)-methyl *p*-nitrobenzohydroximate, 64025-03-2; sodium ethoxide, 141-52-6; sodium methoxide, 124-41-4; acrylonitrile, 107-13-1.

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Neighboring Group Interaction in Ortho-Substituted Aminopyridines. Pyridopyrimidines and Related Systems[1]

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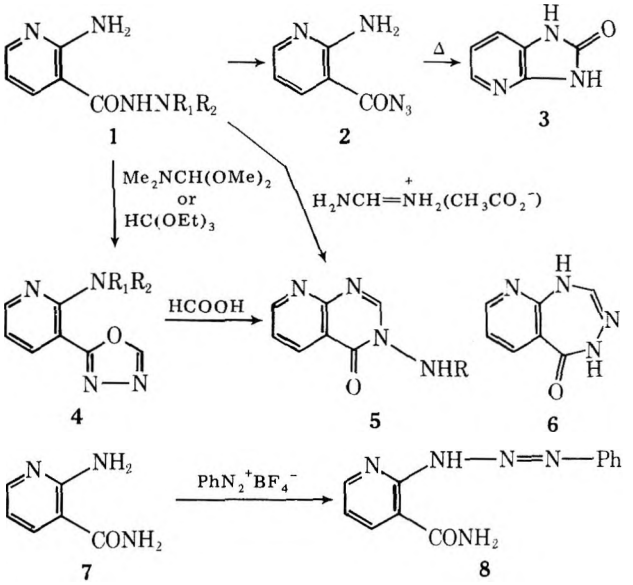
Received June 28, 1977

Hydrazides of isomeric o-aminopyridinecarboxylic acids have been used for syntheses of various bicyclic heterocycles. Derivatives of pyrido[2,3-*d*]-, pyrido[3,2-*d*]- or pyrido[3,4-*d*]pyrimidine, pyrido[3,2-*d*]- or pyrido[3,4-*d*]-*v*-triazine, and pyrazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidine have been prepared. Some other transformations are also described.

Our recent interest in pyridopyrimidines[2,3] and related systems prompted us to investigate these systems and, in particular, some aspects of their preparation. Many synthetic approaches have been reported,[4] but in view of our recent findings it seemed worthwile to explore the possibilities of application of either *N,N*-dimethylaminomethylene derivatives[5-9] or participation of diazo or azido groups[10-19] in the construction of these bicyclic heterocycles. *N,N*-Dimethylformamide dimethyl acetal has been frequently used as a methine group source for various ring closures.

As starting material we have used hydrazides of 2-aminonicotinic acid, 3-aminopicolinic acid, and 3-aminoisonicotinic acid. 2-Aminopyridine-3-carboxylic acid hydrazide (**1**, $R_1 = R_2 = H$) was transformed with either isoamyl nitrite or benzenediazonium tetrafluoroborate under the conditions for azo-transfer reaction[13] into the acyl azide **2**, which was thermally converted into imidazo[4,5-*b*]pyridin-2-one (**3**). This transformation is an example of a Curtius rearrangement with subsequent intramolecular cyclization involving the isocyanato and o-amino groups. By monitoring this rearrangement in a NMR probe, the reaction is shown to be completed in 40 min at 80 °C. The hydrazide, when heated with either *N,N*-dimethylformamide dimethyl acetal or triethyl orthoformate, was transformed into an oxadiazolylpyridine (**4**, $R_1 = R_2 = H$). In the IR spectrum there was no evidence for a carbonyl group, and the NMR spectrum also revealed, in addition to three vicinal pyridine protons, a signal at δ 9.35, arising apparently from a CH group. In the literature, chemical shifts of few



1,3,4-oxadiazoles[20,21] and pyridopyrimidones[4] are recorded, and a differentiation between a H_2 of the oxadiazole system or a H_2 of the pyridopyrimidinone system is not reliable. On the basis of theoretical considerations and the determined molecular weight (162 g), besides the oxadiazole derivative (**4**), two other structures, i.e., the pyrido[2,3-*d*]pyrimidine (**5**,

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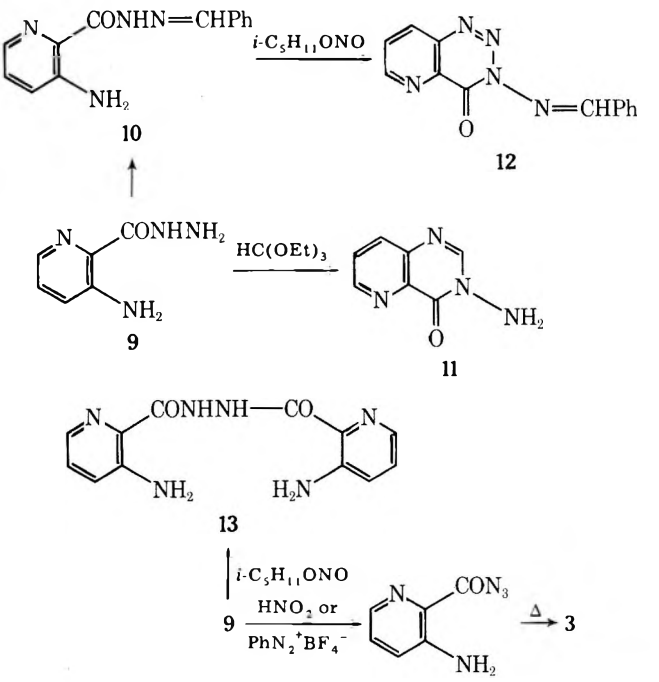
R = H) and pyridotriazepine (**6**), are also possible. Structure **5** is excluded since we have prepared this compound earlier,[3] and structure **6** can also be eliminated because of IR spectroscopic evidence and transformations which are described further. Also, it should be mentioned that benzo-1,3,4-triazepin-5-ones are readily rearranged into derivatives of 3-aminoquinazolin-4-one.[22]

The oxadiazolypyridine (**4**, $R_1 = R_2 = H$) afforded with excess *N,N*-dimethylformamide dimethyl acetal the corresponding *N,N*-dimethylaminomethylene derivative (**4**, $R_1R_2 = CHNMe_2$), whereas with hot formic acid it was transformed into the pyridopyrimidinone (**5**, R = H). This compound could be prepared also from **1** ($R_1 = R_2 = H$) and formamidine acetate directly. The transformation of **4** into **5** takes place most probably via the ring-opened product, i.e., **1**, since it is known that oxadiazoles are cleaved by acids,[21] and cyclization of *o*-aminobenzoic acid hydrazide with formic acid to 3-aminoquinazolin-4-one is well-known.[23] Although pyrido[2,3-*d*]-pyrimidine and some of its derivatives are readily hydrolyzed in acid solution to substituted pyridines,[21] compound **5** (R = H) could be formylated at the 3-amino group in a normal way to give the 3-formylamino compound (**5**, R = HCO). In this connection, it is noteworthy to mention that o-aminobenzoic acid hydrazide when heated with either *N,N*-dimethylformamide dimethyl acetal or triethyl orthoformate is converted to 3-aminoquinazolin-4-one. It has been reported previously[23] that this hydrazide is transformed with triethyl orthoformate into 3-ethoxymethyleneaminoquinazolin-4-one.

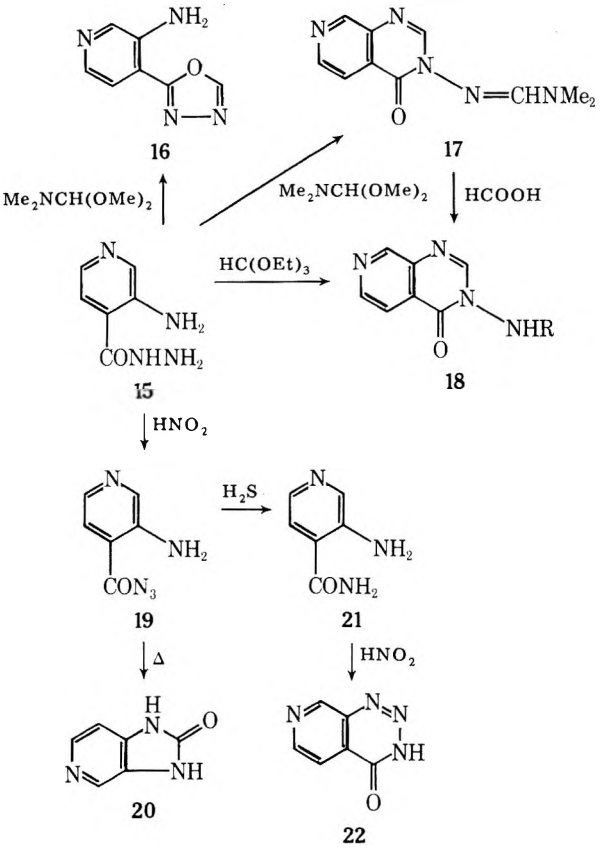
In view of our previous interest in barriers to rotation in some *N'*-heteroaryl *N,N*-dimethylformamidines,[8] we have examined compound **4** ($R_1R_2 = CHNMe_2$). The chemical shift of H_2 at the oxadiazole ring in **4** is dependent on the size of the ortho group in the pyridine part of the molecule. When this group is small, as in the case of an amino group (**4**, $R_1 = R_2 = H$), the oxadiazole ring appears to be coplanar with the pyridine ring (the signal for H_2 of the oxadiazole appears at δ 9.35). If the ortho group is bigger, such as formylamino (**4**, $R_1 = H$, $R_2 = HCO$) or *N,N*-dimethylaminomethyleneamino (**4**, $R_1R_2 = CHNMe_2$), the oxadiazole ring is no longer coplanar with the pyridine ring, and the signal for H_2 of the oxadiazole ring appears at δ 8.15 and 8.62, respectively. This steric hindrance is also reflected in the magnitude of barriers to rotation which is 12.5 kcal/mol for **4** ($R_1R_2 = CHNMe_2$) when compared to 16 kcal/mol for 2-(*N,N*-dimethylaminomethyleneamino)-pyridine and its 3-methyl derivative.[8]

We have reported previously on the synthesis of pyrido[3,2-*d*]-*v*-triazin-4-one,[24] and therefore syntheses of the isomeric systems were tempting. from 2-aminonicotinamide, if diazotized in the usual manner, an easily hydrolyzable diazonium group is generated, and therefore the desired and unknown pyrido[2,3-*d*]-*v*-triazin-4-one is not produced. Therefore, we have attempted to prepare this system from **7** using the aza-transfer reaction with benzenediazonium tetrafluoroborate. However, only the corresponding stable triazene (**8**) could be isolated.

The isomeric 3-aminopyridine-2-carboxylic acid hydrazide (**9**) reacted with *N,N*-dimethylformamide dimethyl acetal to yield the *N,N*-dimethylaminomethylene derivative of **9**, whereas with triethyl orthoformate, 3-aminopyrido[3,2-*d*]-pyrimidin-4-one (**11**) was formed. In nitrosation of **9** with isoamyl nitrite, the desired azide (**14**) was not obtained but the corresponding bishydrazide (**13**) was obtained, apparently by the nitrite ion functioning as an oxidant. Similar conversions with other mild oxidants are known.[25-28] Azide **14** could be obtained with sodium nitrite in acetic acid or by aza transfer from a benzenediazonium ion, and it could be rearranged to **3**. If the benzylidene derivative (**10**) was first prepared from **9** and then diazotized, the *v*-triazine (**12**) could be obtained in good yield.



Synthetic approaches for the preparation of another system, pyrido[3,4-*d*]pyrimidine, were also investigated since there are not many reports regarding this bicyclic system. The hydrazide (**15**) gave with *N,N*-dimethylformamide dimethyl acetal either the oxadiazolylpyridine (**16**) or compound **17**.



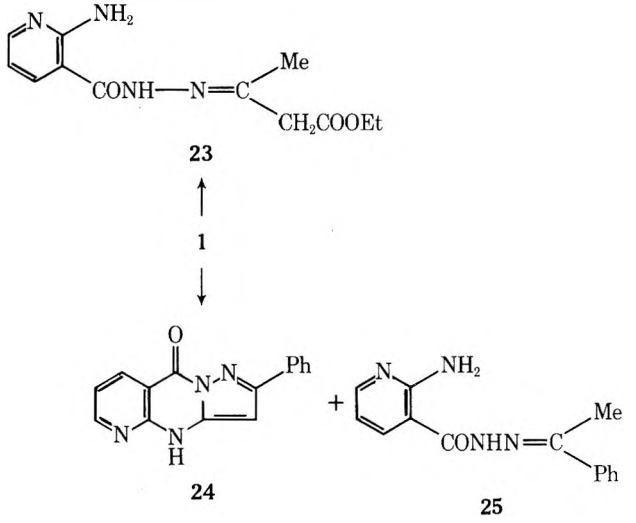
The reaction with triethyl orthoformate proceeded differently, and 3-aminopyrido[3,4-*d*]pyrimidin-4-one (**18**, R = H) could be prepared in moderate yield. This compound was prepared also from ethyl 3-aminopyridine-4-carboxylate and *N,N*-dimethylformamide dimethyl acetal. The intermediate *N,N*-dimethylaminomethylene derivative was not isolated in pure form and was immediately transformed with hydrazine into the bicyclic compound (**18**, R = H). This is an example of dimethylamine as a leaving group, and this contrasts

the known methods of cyclization where an acyl group is eliminated. Compound **17** is transformed with formic acid into the formylamino derivative (**18**, R = HCO), obtainable also by direct formylation of the amine (**18**, R = H).

3-Aminopyridine-4-carboxylic acid azide (**19**) was prepared from **15** and nitrous acid, and on heating it was transformed by Curtius rearrangement into imidazo[4,5-*c*]pyridin-2-one (**20**). The azide was easily transformed with hydrogen sulfide into the amide (**21**), obtainable also under severe reaction conditions from the corresponding ester and ammonia. The easy conversion of the azide into amide is another example of this useful transformation tested already on other compounds.[29] On diazotization the amide (**21**) afforded pyrido[3,4-*d*]-*v*-triazin-4-one (**22**).

In this connection it should be mentioned that the formation of azides **2** and **19** from the corresponding hydrazides contrasts the reactivity of *o*-aminobenzoic acid hydrazide. This, depending upon the acidity of the reaction mixture, is transformed with nitrous acid into either the azide or a mixture of the azide and 3-aminobenzotriazin-4-one.[30,31]

In view of the ready availability of pyrazolo[5,1-*b*]quinazolines from *o*-aminobenzoic acid hydrazides and esters of 1,3-keto carboxylic acids or related compounds with a reactive methylene group,[32] it seemed worthwile to investigate this reaction with the corresponding pyridine analogues. Although the reaction proceeds smoothly in the benzene series, we could only obtain condensation products in the pyridine series in a few cases. The hydrazide (**1**, R = R_1 = H) afforded with ethyl acetoacetate in boiling ethyl acetate only the condensation product (**23**). A similar reaction with ethyl benzoylacetate in



boiling diethylene glycol dimethyl ether gave a mixture of a tricyclic compound (**24**) and a derivative of the so far unknown pyrazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidine system, together with an acyclic compound (**25**) as the major product. The latter compound resulted evidently from condensation, followed by hydrolysis of the ester function and subsequent decarboxylation. The structures of these compounds were ascertained by elemental analyses and spectroscopic evidence.

Experimental Section

Melting points were determined on a Kofler hot-plate melting point apparatus. The NMR spectral measurements were performed on a Jeol JNM C-60 HL spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6L spectrometer.

2-Aminopyridine-3-carboxylic Acid Azide (2). Method A. 2-Aminopyridine-3-carboxylic acid hydrazide[33] (**1**, R_1 = R_2 = H, 0.152 g) was dissolved in glacial acetic acid (5 mL), and isoamyl nitrite (0.12 g) was added slowly while stirring. The reaction mixture was left at room temperature for 12 h and evaporated in vacuo to dryness, and the residue extracted several times with hot *n*-heptane. The product which separated from *n*-heptane on cooling was filtered off: mp 128–130 °C (lit.[34] mp 124 °C), and from the melt new crystals separated, mp 270–273 °C (formation of imidazo[4,5-*b*]pyridin-2-one, **3**); IR 2150 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 8.05 (dd, H_4, $J_{4,5}$ 8.2, $J_{4,6}$ = 2.0 Hz), 6.55 (dd, H_5, $J_{5,6}$ = 5.0 Hz), 8.25 (dd, H_6), 6.9 (broad, NH_2); MS *m/e* 163 (M).

Anal. Calcd for $C_6H_5N_5O$: C, 44.17; H, 3.09; N, 42.93. Found: C, 44.46; H, 3.34; N, 42.75.

The above-mentioned transformation of the azido compound into imidazo[4,5-*b*]pyridin-2-one (**3**) could be followed in a NMR probe. For synthetic purposes, a solution of the azido compound (0.2 g) in diethylene glycol dimethyl ether (5 mL) was heated at 130 °C for 1.5 h. The solvent was evaporated in vacuo and the residue had mp 270–273 °C (lit.[33] mp 270–272 °C); MS *m/e* 135 (M).

Anal. Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.06; H, 3.92; N, 31.42.

Method B. A solution of the hydrazide (**1**, R_1 = R_2 = H, 0.875 g) in dimethyl sulfoxide (10 mL) was treated while stirring with benzendiazonium tetrafluoroborate (1.105 g). After some time, the resulting reddish solution was poured into ice, and the separated solid was filtered off. The crude product was crystallized from water, mp 126 °C (with the formation of bicyclic compound **3**). The compound was found to be identical with that obtained from method A.

2-Amino-3-(1′,3′,4′-oxadiazolyl-5′)pyridine (4, R_1 = R_2 = H). Method A. A mixture of 2-aminopyridine-3-carboxylic acid hydrazide (**1**, R_1 = R_2 = H, 0.75 g), *N,N*-dimethylformamide dimethyl acetal (0.7 g), and diethylene glycol dimethyl ether (20 mL) was heated under reflux for 2 h. On evaporation to dryness in vacuo, the residue was sublimed at 120 °C (0.1 mm) or crystallized from water: yield 0.35 g; mp 162–163 °C; IR (no CO absorption band); ^1H NMR (Me_2SO-d_6) δ 8.10 (dd, H_4, $J_{4,5}$ = 8.1, $J_{4,6}$ = 1.8 Hz), 6.75 (dd, H_5, $J_{5,6}$ = 4.8 Hz), 8.25 (dd, H_6), 9.35 (s, H_2), 7.35 (broad, NH_2); MS *m/e* 162 (M).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.80; H, 4.21; N, 34.31.

Method B. A mixture of the hydrazide (**1**, R_1 = R_2 = H, 0.75 g), triethyl orthoformate (0.75 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 1.5 h. On standing overnight at room temperature and after filtration, the solution was evaporated to dryness in vacuo. The oily residue was treated with water and filtered. On crystallization from water, the product had mp 163 °C (yield 0.33 g) and was found to be identical in all respects with the product obtained as described in method A.

If the crude product from the reaction in method A was crystallized from ethyl acetate, a small amount of a product with mp 246–248 °C separated from the solvent and was identified by the use of analytical data and comparison with an authentic specimen as 3-aminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**5**, R = H) (lit.[3] mp 249–250 °C). The same compound was also obtained if the 2-amino-3-(1′,3′,4′-oxadiazolyl-5′)pyridine (**4**, R_1 = R_2 = H) from method B was heated with excess formic acid under reflux for 1.5 h. On evaporation in vacuo, the residual oil crystallized after some time and was sublimed at 180 °C (0.1 mm) to give pyridopyrimidone **5** (R = H), mp 248 °C.

Finally, 3-aminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**5**, R = H) was also obtained if 2-aminopyridine-3-carboxylic acid hydrazide and formamidine acetate were heated in 2-ethoxyethanol for 2 h and the crude product sublimed at 200 °C (0.1 mm).

2-(*N,N*-Dimethylaminomethyleneamino)-3-(1′,3′,4′-oxadiazolyl-5′)pyridine (4, R_1R_2 = CHNMe$_2$). A mixture of the oxadiazolypyridine (**4**, R_1 = R_2 = H, 0.5 g) and *N,N*-dimethylformamide dimethyl acetal (8 mL) was heated under reflux for 2.5 h. On evaporation in vacuo, the semisolid residue was crystallized from carbon tetrachloride and hexane: yield 0.35 g; mp 90–91 °C; ^1H NMR ($CDCl_3$) δ 8.20 (dd, H_4, $J_{4,5}$ = 7.8, $J_{4,6}$ = 2.0 Hz), 7.01 (dd, H_5, $J_{5,6}$ = 4.8 Hz), 8.48 (dd, H_6), 8.62 (s, H_2 and CH=), 3.10 (s, NMe_2); MS *m/e* 217 (M).

Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.06; H, 5.10; N, 32.42.

3-Formylaminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (5, R = HCO). A mixture of the 3-amino compound (**5**, R = H, 0.4 g), pyridine (1 mL), and formic acid (3 mL of 100%) was heated under reflux for 1 h. The solution was evaporated to dryness in vacuo, and the residue was treated with boiling ethanol. The filtered product had mp 255–263 °C dec; ^1H NMR (Me_2SO-d_6) δ 8.58 (s, H_2), 8.63 (dd, H_5, $J_{5,6}$ = 8.0, $J_{5,7}$ = 2.0 Hz), 7.63 (dd, H_6, $J_{6,7}$ = 4.5 Hz), 9.08 (dd, H_7); MS *m/e* 190 (M).

Anal. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18. Found: C, 50.34; H, 3.40.

Reaction between Anthranilamide and *N,N*-Dimethylformamide Dimethyl Acetal or Triethyl Orthoformate. A mixture of

equivalent amounts of anthranilamide and *N,N*-dimethylformamide dimethyl acetal (or triethyl orthoformate) in diethylene glycol dimethyl ether was heated under reflux for 2 h. The reaction mixture was evaporated to dryness, some 1-propanol was added, and the separated product was filtered off, mp 208–211 °C (lit.[23] mp 202–207 °C from triethyl orthoformate). The compound was found to be identical in all respects with an authentic specimen of 3-aminoquinazolin-4-one.

2-Phenyltriazenylpyridine-3-carboxamide (8). A solution of 2-aminonicotinamide[35] (**7**, 1.37 g) in dimethyl sulfoxide (10 mL) was treated with benzenediazonium tetrafluoroborate (1.92 g). The resulting solution was left at room temperature for 10 min and extracted with diethyl ether (six times with 30 mL). On drying the extracts, the solvent was evaporated, and to the residual oil some water was added. The yellow crystals that formed were filtered off: mp 159–161 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.22 (dd, H_4, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.8 Hz), 7.25 (dd, H_5, $J_{5,6}$ = 5.0 Hz), 8.53 (dd, H_6), 7.9 and 7.5 (m, Ph); MS *m/e* 241 (M).

Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60. Found: c, 60.01; H, 4.82.

The Dimethylaminomethylene Derivative of 3-Aminopyridine-2-carboxylic Acid Hydrazide. A mixture of 3-aminopyridine-2-carboxylic acid hydrazide[33] (**9**, 0.75 g), *N,N*-dimethylformamide dimethyl acetal (0.7 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 2 h. After standing at room temperature overnight, the mixture was evaporated to dryness in vacuo, the residue was dissolved in hot water, and on cooling the product crystallized; yield 0.57 g; mp 82–86 °C (from water); ^{1}H NMR (Me_2SO-d_6) δ 7.10 (m, H_4 and H_5, $J_{4,5}$ = 3.5, $J_{4,6}$ = 2.1, $J_{5,6}$ = 8.4 Hz), 7.74 (dd, H_6), 7.98 (s, N=CH), 2.75 (s, Me); MS *m/e* 207 (M).

Anal. Calcd for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.80. Found: C, 51.98; H, 6.62; N, 33.48.

If, however, instead of the above acetal, triethyl orthoformate was used in the reaction under the same reaction conditions, 3-aminopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**11**) was obtained. The semisolid crude reaction product was treated with a small quantity of hot ethanol and filtered and the residue crystallized from ethanol, mp ~280–285 °C (lit.[3] mp 285–287 °C).

Treatment of 3-Aminopyridine-2-carbohydrazide with Isoamyl Nitrite in Glacial Acetic Acid. Formation of the Bishydrazide (13). A solution of 3-aminopyridine-2-carbohydrazide (**9**, 0.6 g) in glacial acetic acid (10 mL) was treated with isoamyl nitrite (0.47 g), and the yellow solution was left to stand overnight at room temperature. The reaction mixture was diluted with water (70 mL), and the yellow product was filtered and crystallized from ethanol: yield 0.19; mp 227–230 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.90 (dd, H_6), 7.30 (m, H_4 and H_5, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.8, $J_{5,6}$ = 4.0 Hz), 2.80 (broad, NH_2), 10.25 (broad, NH); MS *m/e* 272 (M).

Anal. Calcd for $C_{12}H_{12}N_6O_2$: C, 52.93; H, 4.44; N, 30.87. Found: C, 52.91; H, 4.36; N, 31.13.

If the hydrazide was treated with sodium nitrite in dilute aqueous acetic acid the corresponding azido compound (**14**) could be obtained: mp 135–140 °C (lit.[34] mp 116 °C); ^{1}H NMR (Me_2SO-d_6) δ 8.75 (dd, H_4, $J_{4,5}$ = 9.5, $J_{4,6}$ = 1.8 Hz), 8.25 (dd, H_5, $J_{5,6}$ = 4.5 Hz), 9.28 (dd, H_6); IR 4.68 (N_3), 5.96 μm (CO); MS *m/e* 163 (M), 135 (M − N_2). At the melting point temperature, the compound is transformed into imidazo[4,5-*b*]pyrimidin-2-one (**3**), obtainable also by heating the azido compound in diethylene glycol dimethyl ether for 30 min, mp 275–273 °C (lit.[34] mp 270–272 °C).

The azide is also obtained if a solution of the hydrazide in dimethyl sulfoxide is treated with benzenediazonium tetrafluoroborate and after 30 min the reaction mixture is diluted with water.

The Benzylidene Derivative of 3-Aminopyridine-2-carbohydrazide (10). The hydrazide (0.76 g), benzaldehyde (0.53 g), and 1,2-dimethoxyethane (10 mL) were heated 4 h under reflux. The reaction mixture was evaporated to dryness, and the residue was crystallized from ethanol: yield 0.86 g; mp 170–172 °C; MS *m/e* 240 (M).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.66; H, 5.42; N, 23.10.

The benzylidene derivative of 2-aminopyridine-3-carboxylic acid hydrazide (1, R_1R_2 = CHPh) was prepared in an analogous way from 2-aminopyridine-3-carboxylic acid hydrazide: yield 0.77 g; mp 181 °C (from ethyl acetate and *n*-hexane): MS *m/e* 240 (M).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.68; H, 5.51; N, 23.57.

The Benzylidene Derivative of 3-Aminopyrido[3,2-*d*]-*v*-triazin-4-one (12). A solution of compound **11** (0.24 g) in glacial acetic acid (5 mL) was treated with isoamyl nitrite (0.117 g), and the product which separated was filtered off; yield 0.23 g; mp 207–209 °C (from diethylene glycol dimethyl ether); ^{1}H NMR (Me_2SO-d_6) δ 9.13 (dd, H_6, $J_{6,7}$ = 4.5, $J_{6,8}$ = 1.6 Hz), 8.05 (dd, H_7, $J_{7,8}$ = 8.2 Hz), 8.63 (dd, H_8), 9.22 (s, CH), 8.05 and 7.6 (m, Ph); MS *m/e* 251 (M).

Anal. Calcd for $C_{13}H_9N_5O$: C, 62.14; H, 3.61; N, 27.88. Found: C, 62.42; H, 3.64; N, 27.36.

Reaction between 3-Aminopyridine-4-carboxylic Acid Hydrazide and *N,N*-Dimethylformamide Dimethyl Acetal. Method A. A mixture of the acid hydrazide[33] (**15**, 0.75 g), *N,N*-dimethylformamide dimethyl acetal (0.75 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 2 h. After standing overnight at room temperature, the separated product was filtered off, and the filtrate was evaporated to dryness to give 3-(*N,N*-dimethylaminomethyleneimino)pyrido[3,4-*d*]pyrimidin-4-one (**17**). The combined products were crystallized from water: yield 0.32 g; mp 225 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.44 (s, H_2), 8.0 (dd, H_5, $J_{5,6}$ = 5.0, $J_{5,8}$ = 1.0 Hz), 8.75 (d, H_6), 9.16 (d, H_8), 8.16 (s, N=CH), 3.0 (s, Me); MS *m/e* 217 (M).

Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.73; H, 5.22; N, 32.45.

Method B. If in the above reaction *N,N*-dimethylformamide dimethyl acetal was used in a quantity less than equivalent (0.5 g) to the amount of hydrazide, the obtained product had mp 160 °C (from water) and was identified as 3-amino-4-(1′,3′,4′-oxadiazolyl-5′)pyridine (**16**); ^{1}H NMR (Me_2SO-d_6) δ 8.40 (s, H_2), 7.52 (d, H_5, $J_{5,6}$ = 4.0 Hz), 7.90 (d, H_6), 9.40 (s, H_2); MS *m/e* 162 (M).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found; c, 51.56; H, 4.20; N, 34.62.

3-Aminopyrido[3,4-*d*]pyrimidin-4(3*H*)-one (18). Method A. A mixture of 3-aminopyridine-4-carboxylic acid hydrazide (**15**, 0.75 g), triethyl orthoformate (0.75 g), and diethylene glycol dimethyl ether (10 mL) was heated under reflux for 1.5 h. On evaporation to dryness in vacuo, the semisolid residue was crystallized form ethanol: yield 0.25 g; mp 201 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.60 (s, H_2), 8.10 (dd, H_5, $J_{5,6}$ = 5.4, $J_{5,8}$ = 0.9 Hz), 8.85 (d, H_6), 9.25 (d, H_8); MS *m/e* 162 (M).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.75; N, 34.56. Found: C, 51.95; H, 3.90; N, 34.73.

Method B. A mixture of ethyl 3-aminopyridine-4-carboxylate (1.66 g) and *N,N*-dimethylformamide dimethyl acetal (4 mL) was heated under reflux for 2 h. On evaporation to dryness, the dark oily residue was treated with hydrazine hydrate (2 mL of 100%), and the mixture was heated to boiling for a few minutes. The separated product was filtered off and washed with water, mp 202–205 °C (from ethanol). The compound was found to be identical in all respects with the product obtained as described in method A.

3-Formylaminopyrido[3,4-*d*]pyrimidin-4(3*H*)-one (18, R = HCO). Method A. A mixture of compound **17** (0.25 g) and formic acid (5 mL of 85%) was heated under reflux for 1 h and evaporated to dryness. The residue was treated with ethyl acetate (7 mL) and heated to boiling for a few minutes. On filtration the residue had mp 226–231 °C (0.11 g); ^{1}H NMR (Me_2SO-d_6) δ 8.57 (s, H_2), 8.10 (dd, H_5, $J_{5,6}$ = 5.2, $J_{5,8}$ = 0.9 Hz), 8.83 (d, H_6), 9.20 (d, H_8), 8.48 (s, CH); MS *m/e* 190 (M).

Anal. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.65; H, 3.25; N, 29.30.

Method B. A mixture of 3-aminopyrido[3,4-*d*]pyrimidin-4(3*H*)-one (**18**, R = H, 0.4 g), pyridine (1 mL), and formic acid (3 mL of 100%) was heated under reflux for 2 h. On evaporation to dryness in vacuo, the residue was crystallized from methanol, mp 228–230 °C. The compound was found to be identical in all respects with the product obtained as described in method A.

3-Aminopyridine-4-carboxylic Acid Azide (19). A cold solution of 3-aminopyridine-4-carboxylic acid hydrazide (**15**, 1.0 g) in aqueous acetic acid (12 mL of 25%) was treated with sodium nitrite (0.46 g). The product which separated was filtered off and dried: mp 120–130 °C, with formation of a new compound (**20**) with mp 315 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 8.30 (s, H_2), 7.33 (d, H_5, $J_{5,6}$ = 5.0 Hz), 7.70 (d, H_6); MS *m/e* 163 (M), 135 (M − N_2).

Anal. Calcd for $C_6H_5N_5O$: C, 44.17; H, 3.09. Found: C, 44.32; H, 3.01.

Imidazo[4,5-c]pyridin-2-one (**20**) was prepared from the above compound (**19**) by heating it in diethylene glycol dimethyl ether: mp 315 °C dec (lit.[36] mp 304–305 °C); ^{1}H NMR (M_2SO-d_6) δ 8.18 (d, H_4, $J_{4,7}$ = 0.7 Hz), 8.07 (d, H_6, $J_{6,7}$ = 5.3 Hz), 6.95 (dd, H_7); MS *m/e* 135 (M).

Anal. Calcd for $C_8H_5N_3O$: C, 53.33; H, 3.73. Found: C, 53.11; H, 4.12.

3-Aminopyridine-4-carboxylic Acid Amide (21). Method A. Ethyl 3-aminopyridine-4-carboxylate (2 g) and liquid ammonia (20 mL) were heated in an autoclave at 130 °C for 7 h. The crude product

was sublimed in vacuo to give the pure amide: mp 149 °C (lit.[37] mp 151–152 °C); MS *m/e* 137 (M).

Anal. Calcd for $C_6H_7N_3O$: C, 52.54; H, 5.15. Found: C, 52.66; H, 5.12.

Method B. Into a solution of 3-aminopyridine-4-carboxylic acid azide (**19**, 0.15 g) in ethanol (5 mL) hydrogen sulfide was introduced for 30 min. The precipitated sulfur was filtered off, and the solution was evaporated to dryness to give the amide, mp 148 °C. The compound was found to be identical in all respects with the product obtained as described in method A.

Pyrido[3,4-*d*]-*v*-triazin-4(3*H*)-one (22). A solution of the above amide (**21**, 0.137 g) in glacial acetic acid (5 mL) was treated with sodium nitrite (69 mg) in a little water while stirring. The product which separated was filtered off and had mp 251 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 8.14 (dd, H_5, $J_{5,6}$ = 5.1, $J_{5,8}$ = 0.9 Hz), 9.11 (d, H_6), 9.64 (d, H_8); MS *m/e* 148 (M).

Anal. Calcd for $C_6H_4N_4O$: C, 48.65; H, 2.72. Found: C, 49.03; H, 2.99.

Reaction between 2-Aminopyridine-3-carboxylic Acid Hydrazide and Ethyl Acetoacetate to Give 23. 2-Aminonicotinic acid hydrazide (**1**, 0.5 g), ethyl acetoacetate (0.43 g), ethyl acetate (60 mL), and a drop of triethylamine were heated under reflux for 3 h. The reaction mixture was evaporated to dryness in vacuo, the residue was treated with benzene, and the separated product was filtered off and crystallized from benzene: yield 0.45 g; mp 99–101 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.75 (dd, H_4, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.8 Hz.), 6.60 (dd, H_5, $J_{5,6}$ = 5.0 Hz), 8.17 (dd, H_6), 2.0 (s, Me), 3.40 (s, CH_2CO_2Et).

Anal. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.55; H, 6.10; N, 21.10. Found: C, 55.01; H, 6.47; N, 21.01.

Reaction between 2-Aminopyridine-3-carboxylic Acid Hydrazide and Ethyl Benzoylacetate. A mixture of the hydrazide (**1**, 0.5 g), ethyl benzoylacetate (0.65 g), and diethylene glycol dimethyl ether (10 mL) was heated at 160 °C for 2 h. After about 1 h of heating, crystals started to separate. The product was filtered off and had mp over 290 °C (yield 0.11 g). The tricyclic product (**24**) showed the following spectrum: ^{1}H NMR (Me_2SO-d_6, 147 °C) δ 6.45 (s, H_3), 8.85 (dd, H_6, $J_{6,7}$ = 4.0, $J_{6,8}$ = 1.8 Hz), 8.40 (dd, H_7, $J_{7,8}$ = 8.0 Hz), 8.70 (dd, H_8), 8.10 and 7.5 (m, Ph).

Anal. Calcd for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.37. Found: C, 68.51; H, 4.30; N, 21.19.

The filtrate was evaporated in vacuo to dryness, and the residue was suspended in *n*-hexane, filtered, and washed with ethanol. The product (**25**) was crystallized from ethanol: yield 0.45; mp 209–212 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.85 (dd, H_4, $J_{4,5}$ = 7.5, $J_{4,6}$ = 1.8 Hz), 6.75 (dd, H_5, $J_{5,6}$ = 4.5 Hz), 8.10 (dd, H_6), 2.30 (s, Me), 7.85 and 7.4 (m, Ph).

Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 65.99; H, 5.08; N, 21.65.

Registry No.—**1** (R_1 = R_2 = H), 5327-31-1; **1** (R_1R_2 = CHPh), 64189-07-7; **2**, 64189-06-6; **3**, 16328-62-4; **4**, (R_1 = R_2 = H), 64189-05-5; **4** (R_1R_2 = $CHNMe_2$), 64189-04-4; **5** (R = H), 37554-48-6; **5** (R = HCO), 64189-03-3; **7**, 13438-65-8; **8**, 64189-01-1; **9**, 3303-28-4; **10**, 64201-58-7; **11**, 37554-49-7; **12**, 64189-02-2; **13**, 64189-10-2; **14**, 64189-09-9; **15**, 64189-08-8; **16**, 64188-99-4; **17**, 64189-00-0; **18** (R = H), 64201-55-4; **18** (R = HCO), 64201-57-6; **19**, 64188-98-3; **20**, 7397-68-4; **21**, 64188-97-2; **22**, 64188-96-1; **23**, 64188-95-0; **24**, 64188-94-9; **25**, 64188-93-8; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; formic acid, 64-18-6; anthranilamide, 88-68-6; triethyl orthoformate, 122-51-0; 9-dimethylaminomethylene derivative, 64188-92-7; benzenediazonium tetrafluoroborate, 369-57-3; benzaldehyde, 100-52-7; ethyl 3-aminopyridine-4-carboxylate, 14208-83-4; ethyl acetoacetate, 141-97-9; ethyl benzoylacetate, 94-02-0.

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Stable Arene Imines

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Received June 13, 1977

The syntheses of stable *N*-alkyl arene imines are described. The general route to 1-butyl-, 1-cyclohexyl-, and 1-benzyl-1a,9b-dihydrophenthr[9,10-*b*]azirine includes the reaction of phenanthrene 9,10-oxide with the appropriate amine followed by cyclodehydration of the amino alcohol with PPh_3–CCl_4 reagent. The preparation of 1-acetyl-1a,11b-dihydrochrysen[5,6-*b*]azirine from *trans*-6-acethoxy-5-acetylamino-5,6-dihydrochrysene and NaH is described as an example of an unstable arene imine that rearranges at room temperature to the corresponding *N*-acetyl aryl amine.

It is widely accepted that polycyclic aromatic hydrocarbons exert their carcinogenic properties through metabolically induced binding to tissue constituents.[1] Arene oxides are generally described as the primary intermediates that alkylate amino acid and nucleic acid residues to form hydrocarbon-bound cell substances with new C–O, C–S, or C–N linkages.[2]

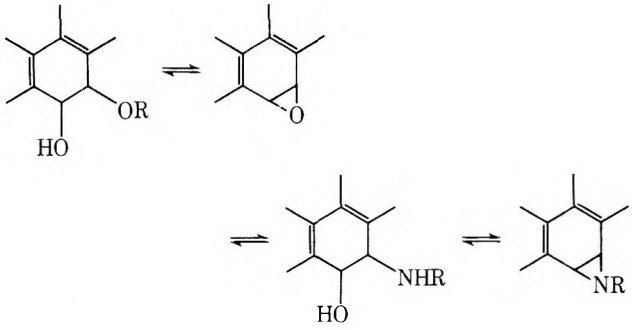
0022-3263/78/1943-0397$01.00/0

Table I. ^{1}H NMR Spectra of some 10-Alkylamino-9,10-dihydrophenanthr-9-ols (2)[a,b]

Compd 2, R =	Registry no.	Chemical shifts, δ (ppm) $H_{(9)}$	$H_{(10)}$	Alkyl protons
n-Butyl[c]	64188-67-6	4.62 (d)	3.74 (d, $J_{9,10}$ = 7 Hz)	2.50 (t, J = 8 Hz, N-CH_2), 1.10–1.68 [m, $(CH_2)_2$], 0.88 (t, J = 5 Hz, CH_3)
tert-Butyl	64188-57-4	4.10 (d)	3.52 (d, $J_{9,10}$ = 10 Hz)	1.50 (s, CH_3)
Cyclohexyl	64188-68-7	4.36 (d)	3.72 (d, $J_{9,10}$ = 10 Hz)	2.42 (m, N-CH), 0.85–1.92 (m, cyclohexyl)
Benzyl	64188-69-8	4.52 (d)	3.68 (d, $J_{9,10}$ = 8 Hz)	3.81 (s, N-CH_2)

[a] In $CDCl_3$ + Me_4Si. [b] The NH and OH protons appear as broad signals between 2.40 and 2.80 ppm. [c] This compound has been reported by Dey and Neumeyer (ref 18).

Chart I

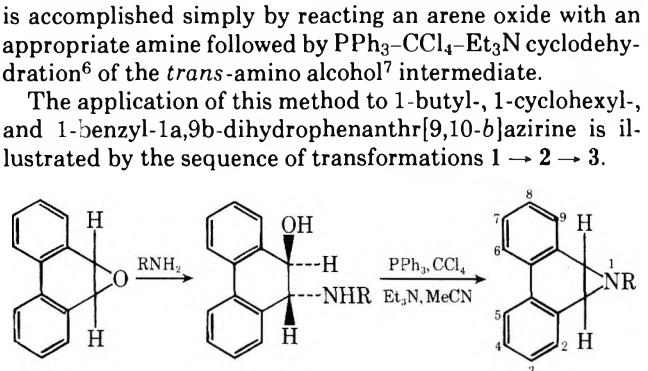


R = peptide or nucleic acid residue

Thus, upon reversing these alkylations there may be formed not only the original arene oxides, but also the analogous arene imines (Chart I). This hypothesis concerning the existence of aziridines as transient intermediates in chemical carcinogenesis finds some support in the observation that β-amino alcohols can be metabolized to aziridines.[3]

Recently,[4] we announced briefly the synthesis of the first *N*-acetylphenanthrene imine and Shudo and Okamoto[5] reported the corresponding *N*-tosyl derivative. Imines of higher polycyclic hydrocarbons were prepared as well (vide infra). However, these compounds which have electron-attracting groups attached to the nitrogen atom proved to rearrange readily at ambient temperature to aromatic amines and are therefore unsuitable for biological tests. In this study, we find that arene imines which have electron-donating substituents on the aziridine nitrogen are perfectly stable. The synthesis is accomplished simply by reacting an arene oxide with an appropriate amine followed by PPh_3–CCl_4–Et_3N cyclodehydration[6] of the *trans*-amino alcohol[7] intermediate.

The application of this method to 1-butyl-, 1-cyclohexyl-, and 1-benzyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine is illustrated by the sequence of transformations **1** → **2** → **3**.

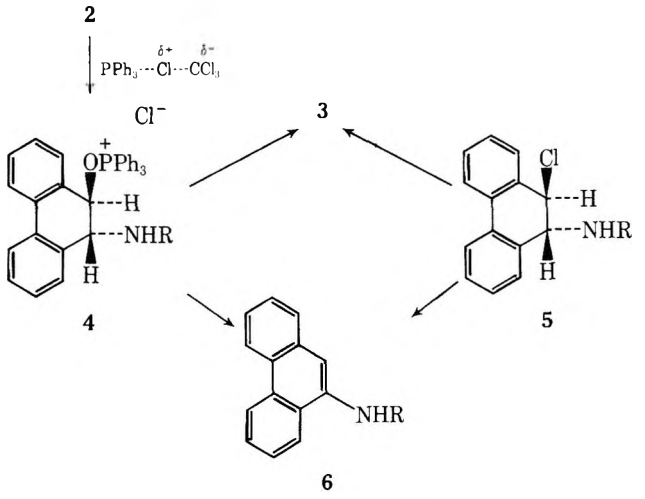


a, R = *n*-butyl
b, R = cyclohexyl
c, R = benzyl

While the first step seems to be hardly affected by the geometry of the amine, conversion of **2** into **3** is very sensitive to steric effects so that 10-*tert*-butylamino-9,10-dihydrophenanthr-9-ol [**2**, R = $C(CH_3)_3$] fails to cyclize to the respective aziridine.

Attempts to obtain **3** by a stepwise transformation of **2** to haloamine **5**, followed by cyclodehydrohalogenation, resulted in rapid aromatization to the substituted 9-aminophenanthrene (**6**). This provides support for the mechanism proposed by Appel and Kleinstück[6] which does not include a 10-halogeno-9-amine-9,10-dihydrophenanthrene intermediate (Chart II). Small amounts of *N*-alkyl-9-aminophenanthrenes (**6**) that were obtained as side products are assumed to be formed by HCl addition to **3** or, more likely, by loss of triphenylphosphine oxide from intermediate **4**.

Chart II



The structures of the amino alcohols **2** and the imines **3** were deduced from the elementary and spectral analyses. The most indicative feature of the mass spectra of both compounds **2** and **3** is the intense fluorenyl peak (usually base peak) *m/e* 165. This ion is characteristic for 9,10-dihydrophenanthrene derivatives but is absent in the fully aromatic system.[8] While the aziridines **3** form distinctive molecular ions, the amino alcohols readily loose water and give $[M - H_2O]^{+\cdot}$ ions which are more abundant than $M^{+\cdot}$.

Some ^{1}H NMR data for compounds **2** and **3** are listed in Tables I and II. As expected, the chemical shift of $H_{(9)}$ in **2** is sensitive to the geometry of the polycyclic system. The magnetic anisotropy effect is less pronounced in the distorted *N*-*tert*-butyl- and *N*-cyclohexylamino alcohols than in **3a** and **3c**.

The ring protons in the rigid arene imines **3** resonate at lower field than those of flexible aziridines. While, e.g., *cis*-1-ethyl-2,3-diphenylaziridine shows up at ~2.79 ppm,[9] the peaks of $H_{(1a)}$ and $H_{(9b)}$ of **3a–c** are below 2.97 ppm. This deshielding is somewhat smaller than reported[10] for the corresponding oxiranes (the oxirane protons of phenanthrene 9,10-oxide and *cis*-stilbene oxide resonate at 4.67 and 4.19 ppm, respectively[10]) owing to the greater interaction of the nitrogen lone pair with the aromatic π electrons.

The aromatic protons in phenanthrene-9,10-imines (**3**) show two well-separated multiplets of which the low-field complex is assigned to $H_{(5)}$ and $H_{(6)}$.

The high-field absorption (2.05 ppm) of the α-*N*-cyclohexyl

Table II. ^{1}H NMR, UV, and Mass Spectra of some 1-Alkyl-1a,9b-dihydrophenanthr[9,10-*b*]azirines (3)

Compd	Registry no.	^{1}H NMR, δ (ppm)[a]	UV λ_{max}, nm (log ϵ)[b]	Major fragment ions *m/e* (rel intensity)
3a	64188-66-5	0.88 (t, J = 5 Hz, CH_3), 1.20–1.72 [m, $(CH_2)_2$], 2.54 (t, J = 8 Hz, N-CH_2), 2.97 (s, $H_{(1a,9b)}$) 7.94 (m, $H_{(5,6)}$)	239 (3.82), 271 (3.99), 277 (4.01), 281 (4.00), 288 (3.68), 295 (3.67), 306 (3.58)	249 (60), 206 (100), 178 (31), 165 (30)
3b	64188-65-4	1.00–2.00 (m, cyclohexyl), 2.05 (m, N-CH_2), 3.03 (s, $H_{(1a,9b)}$), 7.96 (m, $H_{(5,6)}$)	242 (3.58), 269 (3.99), 274 (4.00), 280 (3.99), 287 (3.86), 292 (3.69), 305 (3.50)	275 (76), 232 (38), 178 (62), 165 (100)
3c	64188-64-3	3.19 (s, $H_{(1a,9b)}$), 3.75 (s, N-CH_2), 8.04 (m, $H_{(5,6)}$)	225 (4.10), 239 (3.86), 272 (3.96), 275 (3.97), 281 (3.95), 288 (3.80), 295 (3.64), 305 (3.49)	283 (100), 192 (86), 178 (77), 165 (94)

[a] In $CDCl_3$ + Me_4Si. [b] Compound **3a** and **3c** were recorded in cyclohexane and **3b** in $CHCl_3$.

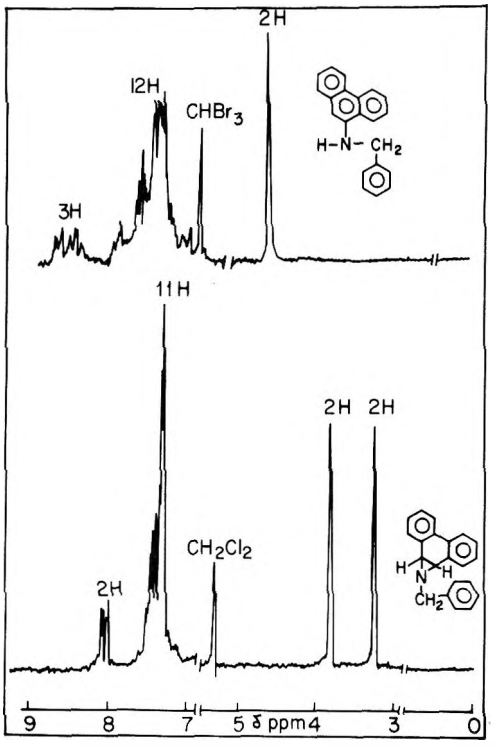


Figure 1. 100-MHz ^{1}H NMR spectra of 1-benzyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine (**3c**) at 31 °C in CD_2Cl_2, and (after rearrangement) at 140 °C in $CDBr_3$.

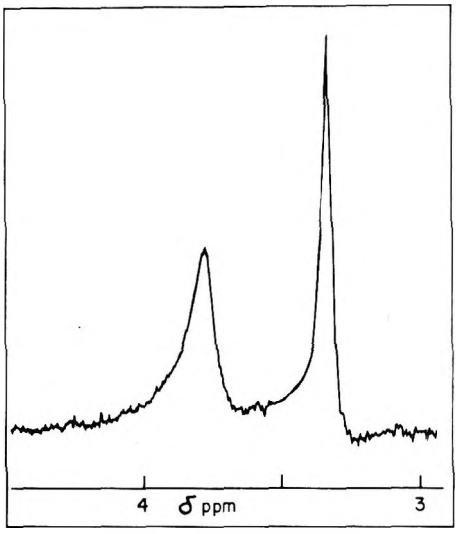
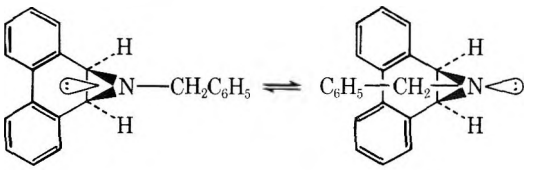


Figure 2. ^{1}H NMR signals of $H_{1a}H_{9b}$ (narrow line) and benzylic protons (broad peak) of **3c** at −98 °C.

proton of **3b** exceeds the upper-field limit for an equatorial cyclohexylamine hydrogen.[11] Since the flexibility of the heavily substituted cyclohexane ring is rather restricted, it may be suggested that the nitrogen (and the aziridine ring) is virtually equatorial.

The assignment of the two singlets (3.19 and 3.75 ppm) in the ^{1}H NMR spectrum of 1-benzyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine (**3c**) (Figure 1) was accomplished by the aid of ^{13}C NMR spectroscopy. The aziridine ring and methylene carbon atoms resonate at δ 48.97 and 67.75 ppm, respectively. On off-resonance decoupling $C_{(1a)}$ and $C_{(9b)}$ appear as a doublet, while the benzylic CH_2 carbon forms a triplet. Thus, by off-resonance decoupling techniques at various decoupler offsets the ^{1}H NMR peak at 3.75 ppm is found, unequivocally, to arise from the methylene, and the singlet at 3.19 ppm arises from the vicinal aziridine-ring protons. Further confirmation to this assignment is obtained from the ^{1}H NMR spectra of **3a** and **3b** which have only one singlet in the vicinity of 3 ppm.

The CH_2 signals of **3c** in both ^{1}H and ^{13}C NMR spectra broaden upon lowering the temperature. The effect on the ^{1}H NMR singlet is larger than on the ^{13}C peak (see Figure 2). This phenomenon is attributed to inversion of the aziridine nitrogen by which a mixture of the two invertomers **7** and **8** result.



7 **8**

Owing to symmetry factors associated with the *cis*-aziridine structure, the $CH_{(1a)}$ and $CH_{(9b)}$ peaks remain almost unchanged. It may thus be concluded that the reason for the line broadening is not just a viscosity effect. The chemical shift (3.75 ppm) reflects, therefore, the relative contribution of the exo and endo structures **7** and **8** to the equilibrium mixture.

Solvent effect on the ^{1}H NMR spectrum of **3c** has been studied and deserves some attention. Deuterated benzene, toluene, as well as CS_2 that have high π-electron densities are assumed to be repelled by the aziridine nitrogen lone pair.[12] Thus, an approach of the solvent from the opposite direction shields the aziridine protons (see Table III). The effect is largest in $CD_3C_6D_5$ (hyperconjugation) and smallest in the relative π-electron poor CS_2. The opposite effect of C_5D_5N can

Table III. ^{1}H NMR Spectra of 1-Benzyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine (3c) in Various Solvents at 100 MHz

Solvent	$H_{(1a,9b)}$[a]	$\Delta H_{(1a,9b)}$[b]	CH_2[a]	ΔCH_2[b]	$H_{(5,6)}$[a]	$\Delta H_{(5,6)}$[b]
CCl_4	300.9	0	370.2	0	797.0	0
$CDCl_3$	318.8	+17.9	382.1	+11.0	795.9	−1.1
CD_2Cl_2	318.0	+17.1	375.1	+4.9	801.1	+4.1
CS_2	296.4	−5.6	364.5	−5.7	786.6	−10.4
C_6D_6	277.6	−22.3	345.1	−24.7	783.3	−13.7
C_7D_8	274.6	−25.3	343.6	−26.6	773.1	−23.9
C_5D_5N	328.8	+27.3	377.1	+6.9	812.2	+15.2

[a] Chemical shifts in Hz from Me_4Si internal reference. [b] As compared with CCl_4.

be rationalized by the considerable accumulation of positive charge on $C_{(2)}$ and $C_{(6)}$ of the pyridine molecule. This causes attraction of the solvent by the aziridine lone pair and deshielding of the ring protons. The effect of $CDCl_3$ on aziridine ^{1}H NMR has been well documented.[13] The CCl_3 group is linked via a D bond to the nonbonding orbital and causes moderate *deshielding*. A similar effect is observed in CD_2Cl_2.

As noted, the *N*-alkyl arene imines **3a–c** are stable and do not rearrange below 100 °C. However, at 114 °C (in $CDBr_3$) the ^{1}H NMR indicates slow conversion into 9-aminophenanthrenes. At 140 °C the aromatization is instantaneous (see Figure 1).

It is remarkable that the *N*-alkyl arene imines are also stable toward strong acids. ^{1}H NMR measurements conducted in $CDCl_3/CF_3COOH$ at room temperature indicate protonation of the nitrogen atom without ring opening. The corresponding chemical shifts for (a) *N*-butyl- and (b) *N*-cyclohexyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine are (a) δ 0.95 (t, 3, J = 4 Hz), 1.17–1.96 (m, 4), 3.36 (m, 2), 4.59 (d, J = 3 Hz), 6.33 (1, m), 7.32–8.12 (m, 8); and (b) 1.14–2.36 (m, 10), 2.74 (m, 1), 4.59 (s, 2), 6.55 (m, 1), 7.42–8.07 (m, 8) ppm. The main changes that occur in the UV spectra of imines **3** upon protonation is the disappearance of the 305-nm band and the appearance of a strong absorption at 255–265 nm.

In contrast to *N*-alkyl arene imines, the *N*-acetyl analogues readily rearrange to aromatic *N*-acetylamines. We assume that the difference in stability is associated with the existence of the mesomeric form B shown in Chart III, in which the high order of the imine carbonyl N–C bond has a weakening effect on the ring N–C linkages. In aliphatic aziridines, intermediates of type C usually undergo cyclization to oxazoline derivatives.[14] In the aromatic series, rearrangement to D (tautomers of the *N*-acetyl aryl amine E) predominates due to obvious thermodynamic reasons.

In addition to 1-acetyl-1a,9b-dihydrophenanthr[9,10-*b*]-azirine, which has been announced in our preliminary communication,[4] we attempted the preparation of some higher polycyclic *N*-acetyl arene imines; for example, chrysene-5,6-quinone 5-monoxime (**9**) was reduced with lithium aluminum hydride to 5-amino-5,6-dihydrochrysen-6-ol (**10**). The *N*-acetylamino acetate **11** was then treated at 25 °C with sodium hydride, but the resulting 1-acetyl-1a,11b-dihydrochrysen[5,6-*b*]azirine (**12**) proved to rearrange under these conditions to 6-acetylaminochrysene (**13**) of mp 301 °C[15] (free of any 5-acetylamino isomer of mp 250 °C[16]). The best evidence for the formation of imine **12** was obtained from an experiment in which the cyclodeacetylation of **11** → **12** was carried out in pyridine-d_5 in an NMR tube, and the spectrum of the reaction mixture was recorded on a CFT-20 instrument every 30–70 min. The characteristic bands of **11** at 1.39, 2.42, 2.86, and 6.21 ppm gradually disappeared and the imine spectrum, δ 2.50, 4.33, and 4.55 ppm, was built up. The highest intensities of the peaks of **12** were obtained after 70 min. After this period the spectrum of 6-acetylaminochrysene (**13**) prevailed.

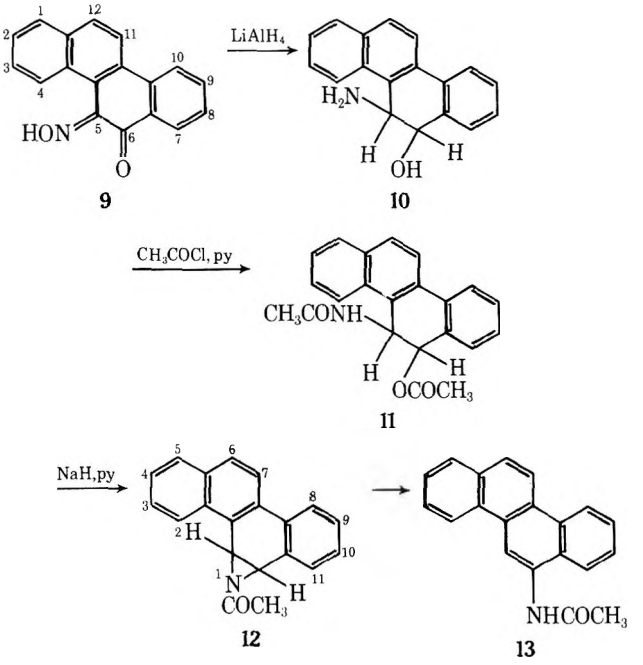
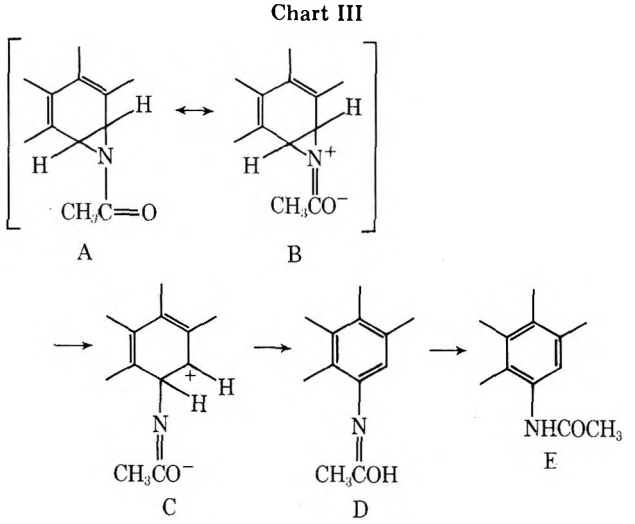


Chart III



The structure of the starting oxime **9** was established by virtue of the significant peak m/e 152 $[C_{10}H_6N]^+$ in the mass spectrum. The second possible isomer, viz., chrysene-5,6-quinone 6-oxime would, by similar fragmentation, give rise to ion $[C_6H_4CN]^+$ of m/e 102 which, however, is not present in the spectrum. It is thus interesting to note that the nitrogen atom migrates from $C_{(5)}$ in the oxime to $C_{(6)}$ in the final acetyl amine derivative. This migration doubtlessly occurs via the cyclic arene imine intermediate.

Experimental Section

General. Melting points were taken either on a Buchi capillary melting point apparatus or on a Fisher hot plate instrument and are

not corrected. Infrared and ultraviolet spectra were obtained on a Perkin-Elmer Model 157 and a Unicam SP-800 spectrophotometer, respectively. Proton magnetic resonance spectra were run using Varian EM-360, HA-100D, and CFT-20 spectrometers. The latter instrument, equipped with a Fourier transformer, was also used for the recording of ^{13}C magnetic resonance spectra. Mass spectra were obtained with the aid of a Varian MAT-311 instrument at 70 eV. Preparative thin-layer chromatography was performed with plates precoated with Merck alumina type T.

10-Benzylamino-9,10-dihydrophenanthr-9-ol (2c). A mixture of 1.94 g (10 mmol) of phenanthrene 9,10-oxide (**1**)[17] and 2.14 g (20 mmol) of benzylamine was stirred at 80–90 °C under N_2 for 6 h. The reaction mixture was left at room temperature for 16 h and excess benzylamine removed in vacuo. The oily residue proved by NMR analysis (see Table I) to be essentially pure. The major fragment ions in the mass spectrum are: *m/e* (rel intensity) 301 (M^+, 19), 283 (69), 194 (59), 165 (100).

When a solution of the amino alcohol in a tenfold volume of EtOH was treated with gaseous HCl, the colorless hydrochloride separated in quantitative yield, mp 226 °C (from acetonitrile). Anal. Calcd for $C_{21}H_{20}ClNO$: C, 74.7; H, 5.9; Cl, 10.5; N, 4.1. Found: C, 74.9; H, 5.9; Cl, 10.5; N, 4.4.

10-*n*-Butylamino-,[18] 10-cyclohexylamino-, and 10-tert-butylamino-9,10-dihydrophenanthr-9-ol were obtained in the same manner by heating **1** in the appropriate amine for 5 h at 75 °C, 5 h at 90 °C, and 48 h at 43 °C, respectively.

1-Benzyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine (3c). To a solution of 301 mg (1 mmol) of **2c** in 1 mL of acetonitrile were added succesively 270 mg (1.2 mmol) of freshly crystallized PPh_3, 0.2 mL of Et_3N, and 0.5 mL of CCl_4 (all solvents were dried and freshly distilled). The mixture was stirred under N_2 at 70 °C for 3 h, and then cooled and left to stand at room temperature for 16 h. Cold water was added to dissolve excess triethylamine and its hydrochloride. The organic layer was diluted with 15 mL of $CHCl_3$, washed twice with cold water, dried (K_2CO_3), and concentrated. Upon addition of ether to the residue, 113 mg of colorless imine separated immediately. A second crop of pale yellow compound was further purified by preperative TLC on Merck alumina type T (hexane–ether mixture, 5:1, served as eluent). The total yield of pure **3c** was 42%, mp 128 °C (from methylcyclohexane). Anal. Calcd for $C_{21}H_{17}N$: C, 89.0; H, 6.0; N, 4.9. Found: C, 89.0; H, 6.3; N, 4.7.

1-Butyl-1a,9b-dihydrophenanthr[9,10-b]azirine (3a) was obtained in 40% yield by the same method, mp 87 °C (from methylcyclohexane). Anal. Calcd for $C_{18}H_{19}N$: C, 86.7; H, 7.6. Found: C, 86.4; H, 7.5. Conversion of **2c** into **1-cyclohexyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine (3b)** was affected similarly but 100% excess PPh_3 and 6 h heating were required, mp 123 °C (from methylcyclohexane). Anal. Calcd for $c_{20}H_{21}N$: C, 87.3; H, 7.6; N, 5.1. Found: C, 87.3; H, 7.4; N, 4.8.

Additional physical data of **3a–c** are listed in Table II.

***trans*-5-Amino-5,6-dihydrochrysen-6-ol (10).** Powdered chrysene-5,6-quinone 5-oxime (**9**)[19] (2.73 g, 10 mmol) was added in small portions under N_2 to a stirred suspension of 1.14 g (30 mmol) of lithium aluminum hydride in 200 mL of dry ether. After the initial exothermic reaction ceased the mixture was refluxed for 6 h, during which the color changed from bright green to dark tan. Excess reagent was decomposed with 5 mL of acetone followed by 100 mL of aqueous sodium tartarate (2 M). The aqueous layer was extracted twice with 100 mL of benzene. The combined organic layers were washed with water, dried (K_2CO_3) and concentrated to a volume of 20 mL. Addition of 25 mL of hexane afforded 1.93 g (74%) of colorless amino alcohol **10**. The analytical sample was recrystallized from a mixture of benzene–hexane: mp 123 °C; IR (Nujol) 3300, 3280, 3200 cm^{-1} (NH, OH); ^1H NMR ($CDCl_3$) δ 2.58 (br s, 3), 4.50 (m, 1), 5.60 (d, 1 J = 5 Hz), 7.60–8.62 ppm (m, 10); MS *m/e* (rel intensity) 261 (M^+, 13), 246 (100), 228 (28), 215 (57). Anal. Calcd for $C_{18}H_{15}NO$: C, 82.8; H, 5.8; N, 5.4. Found: C, 82.5; H, 6.0; N, 5.1.

***trans*-6-Acetoxy-5-acetylamino-5,6-dihydrochrysene (11).** A mixture of 10 mL of acetic anhydride and 15 mL of dry pyridine was refluxed for 15 min and added to a cold solution of 1.30 g (50 mmol) of **10** in 15 mL of pyridine. The mixture was stirred at room temperature for 24 h. The cream-colored precipitate was recrystallized from toluene to yield 1.72 g (100%) of **11**: mp 301 °C; IR (Nujol) 3250 (NH), 1760 (ester carbonyl), 1640 cm^{-1} (amide); UV λ_{max} (log ϵ)(CH_3CN) 256 (4.68), 266 (4.84), 294 (4.06), 305 (4.13), 317 (4.03), 340 nm (2.83); ^1H NMR (pyridine-d_5) δ 1.39 (s, 3), 2.42 (s, 3), 2.86 (m, 1) 4.73 (br s, 2), 6.21 (d, 1 J = 5 Hz), 7.19–8.69 ppm (m, 10); MS *m/e* (rel intensity) 345 (M^+, < 1), 285 (77), 243 (100), 215 (82). Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.5; H, 5.5; N, 4.1. Found: C, 76.0; H, 5.5; N, 4.2.

Reaction of 11 with Sodium Hydride. (a) A mixture of 345 mg (1 mmol) of **11**, 2 mmol of NaH (freshly washed with pentane to remove mineral oil), and 50 mL of pyridine was stirred under N_2 at room temperature for 8 h. Ethanol was added to the green solution to decompose excess NaH. A small amount of solids was removed by filtration, and the filtrate was evaporated under reduced pressure to dryness. The residue was recrystallized from acetic acid to yield 240 mg (84%) of 6-acetylaminochrysene (**13**), mp 300–301 °C (lit.[15] 299.5–301 °C); IR (Nujol) 3240 (NH), 1640 cm^{-1} (amide); ^1H NMR (pyridine-d_5) δ 2.56 (s, 3), 7.56–8.77 ppm (m, 11); MS *m/e* (rel intensity) 285 (M^+ 37), 243 (100), 219 (90). The same result was also obtained when the above reaction mixture was refluxed for 5 min.

(b) A high-precision NMR tube was charged with 2 mg of **11**, 1 mL of pyridine-d_5, and 1 mg of sodium hydride (80% in mineral oil) and sealed under N_2. The ^1H NMR spectrum was recorded on a CFT-20 instrument (with Fourier transformer)(31 °C) every 30–70 min. The initial spectrum consisted of the bands of **11** (vide supra) and those of mineral oil. The second recording indicated new peaks at δ 2.50, 4.33, and 4.55 ppm which are attributed to the acetyl and aziridine-ring protons of **1-acetyl-1a,11b-dihydrochrysen[5,6-*b*]azirine (12)**, as well as small peaks of **13**. After 70 min the spectrum of **12** diminished and that of **13** prevailed. Finally (3 h), only the spectrum of 6-acetylaminochrysene could be observed.

***trans*-9-Acetoxy-10-acetylamino-9,10-dihydrophenanthrene.** *trans*-10-Amino-9,10-dihydrophenanthr-9-ol[4,5] was converted in quantitative yield into the corresponding acetoxyacetylamine by the method described above for **11**: mp 176 °C (from aqueous MeOH); IR (Nujol) 3270 (NH), 1732 (ester carbonyl) 1645 cm^{-1} (amide); UV λ_{max} (log ϵ)(EtOH) 220 (4.72), 273 (4.30), 285 nm (4.08); ^1H NMR ($CDCl_3$) δ 2.10 (s, 6), 5.62 (d, 1 J = 4 Hz), 5.82 (m, 1), 6.10 (d, 1 J = 4 Hz), 7.33–7.93 ppm (m, 8); (C_6D_6) δ 1.28 (s, 3), 1.39 (s, 3), 4.98 (d, 1 J_{CHCH} = 5 Hz), 5.62 (dd, 1 J_{CHCH} = 5, J_{CHNH} = 9 Hz), 6.22 (d, 1 J_{CHCH} = 5 Hz), 7.00–7.60 ppm (m, 8); (pyridine-d_5) δ 0.86 (s, 3), 1.62 (s, 3), 4.23 (br s, 1), 5.37 (dd, 1 J_{CHCH} = 4, J_{CHNH} = 9 Hz), 5.65 (d, 1 J_{CHCH} = 4 Hz), 6.36–7.32 ppm (m, 8); MS *m/e* (rel intensity) 235 (M − CH_3CO_2H, 60), 193 (100), 165 (57). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.1; H, 5.7; N, 4.8.

1-Acetyl-1a,9b-dihydrophenanthr[9,10-*b*]azirine. (a) Cyclodeacetylation with NaH. Small-scale synthesis was carried out in an NMR tube in which 2 mg of the above acetoxyacetylamine was treated with 1 mg of NaH (80%) and 1 mL of pyridine-d_5 as described for the chrysene derivative. The solvent was removed in vacuo immediately after the bands of the starting material have disappeared. The *N*-acetyl protons of the imine show up as a singlet at 1.63 ppm, and the aziridine protons as doublets at 4.10 and 4.93 ppm (J = 4 Hz).[20]

On 1-mmol scale preparation a mixture of 295 mg of the diacetylated amino alcohol, 2 mmol of NaH, and 5 mL of pyridine was stirred for 48 h at room temperature under N_2. However, workup as above afforded the arene imine together with some 9-acetylaminophenanthrene.[21] Anal. Calcd for $C_{16}H_{13}NO$: C, 81.7; H, 5.5; N, 6.0. Found: C, 81.6; H, 5.4; N, 5.5.

(b) Cyclodeacetylation with CH_3Li. At −60 °C under N_2 atmosphere there was injected 1.2 mL of a 1 M solution of CH_3Li in ether into a stirred mixture of 295 mg (1 mmol) of the acetoxyacetylamine in 5 mL of dry THF. The green solution was gradually warmed to room temperature, and the solvents were removed in vacuo. The residue was extracted with $CHCl_3$, dried (K_2CO_3), and concentrated. As in method a, the resulting imine was accompanied with varying amounts of 9-acetylaminophenanthrene.

Acknowledgments. We thank the Ber-Lehmsdorf Foundation for Cancer Research and the Central Func of the Hebrew University for financial support.

Registry No.—**1**, 585-08-0; **2c** HCl, 64188-63-2; **9**, 14140-05-7; **10**, 64188-62-1; **11**, 64188-61-0; **12**, 64188-60-9; **13**, 63018-87-3; 9-benzylaminophenanthrene, 64188-59-6; benzylamine, 100-46-9; *n*-butylamine, 109-73-9; cyclohexylamine, 108-91-8; *tert*-butylamine, 75-64-9; acetic anhydride, 108-24-7; *trans*-9-acetoxy-10-acetylamino-9,10-dihydrophenanthrene, 64188-58-5; *trans*-10-amino-9,10-dihydrophenanthr-9-ol, 60883-94-5; 1-acetyl-1a,9b-dihydrophenanthr[9,10*b*]azinine, 59310-28-0.

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Synthesis and Chemical Properties of α-Alkyl(aryl)thiovinyl Isocyanates

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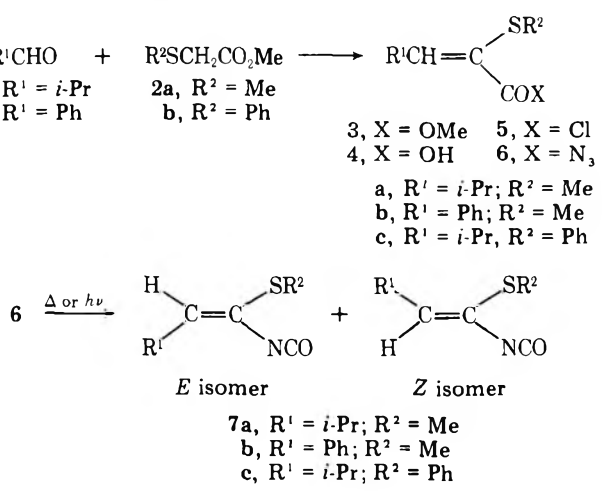
Received June 28, 1977

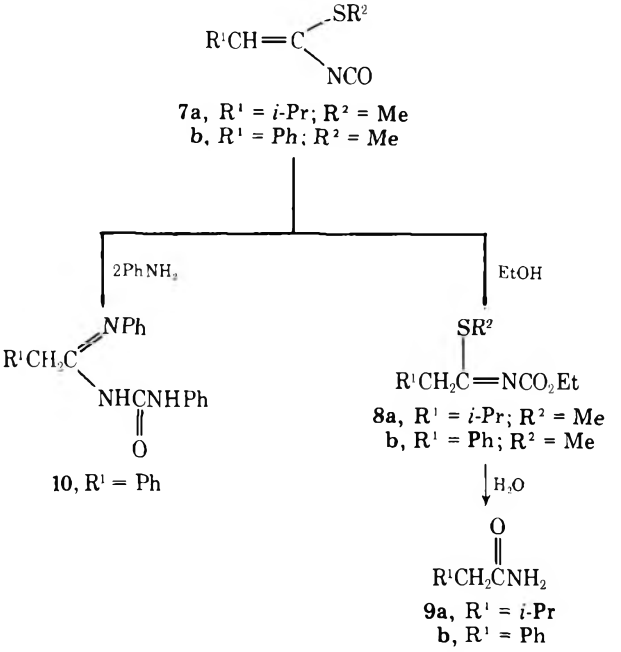
Thermolysis or photolysis of α-alkyl(aryl)thioacrylyl azides **6** gave α-alkyl(aryl)thiovinyl isocyanates **7** in good yields. The isocyanates **7** reacted with aromatic hydrazines to give the triazoles **11** and the triazolinone **12**. In the reaction of **7a** with enamines, the pyridone **15a** or the azadecalin **15b** were isolated. Thermolysis of **7a** gave 4-methylthio-5-isopropyluracil (**16**) quantitatively, while **7b** led to 3-methylthioisocarbostyril (**17**). 3-Methylthio-4-chloroisocarbostyril (**19a**) and 3-methylthio-4-bromoisocarbostyril (**19b**) were obtained by the treatment of **17** with $CuCl_2$–CuO and Br_2–CuO, respectively.

In recent years, the chemical properties of acyl isocyanates have been widely investigated and many heterocyclic compounds were derived from them.[1] In spite of their great synthetic utility, difficulty in the preparation of aliphatic acyl isocyanates[2] and instability of aromatic acyl isocyanates have restricted the utilization of acyl isocyanates. The synthesis of reagents equivalent to acyl isocyanates has been undertaken to overcome these limitations.

Since the vinyl sulfide group is easily converted to the carbonyl group,[3] α-alkyl(aryl)thiovinyl isocyanates are expected to be potentially useful in place of acyl isocyanates in organic synthesis. We also expect them to provide new routes for the synthesis of various heterocyclic compounds containing the sulfide group, since α,β-unsaturated isocyanates have been used in the synthesis of heterocyclic compounds.[4] From these points of view, we wish to report here the synthesis and some chemical properties of α-alkyl(aryl)thiovinyl isocyanates.

Thermolysis or photolysis of a mixture of (*E*)- and (*Z*)-α-alkyl(aryl)thioacrylyl azides **6**, prepared from aldehydes **1** and methyl methyl(phenyl)thioacetates **2**, gave α-alkyl(aryl)-thiovinyl isocyanates **7** in good yields. The structures of **7** were established by spectral data and chemical evidence. The IR spectrum of **7a** displays characteristic absorption bands at 2240 and 1620 cm^{-1} assignable to NCO and olefinic linkage, respectively. The NMR spectrum shows two doublets at 5.17 and 5.40 ppm in the ratio of 87:13. The peak at higher field would be assignable to the vinyl proton of the *E* isomer and the other to that of the *Z* isomer. Treatment of **7a** and **7b** with ethanol gave the amides **9** which were formed from the imino sulfides **8** by hydrolysis. Only **8a** as intermediate was isolated. With aniline, **7b** led to the amidine **10**.





The isocyanate **7a** reacted with *p*-nitrophenylhydrazine at room temperature to give 1-*p*-nitrophenyl-3-hydroxy-5-

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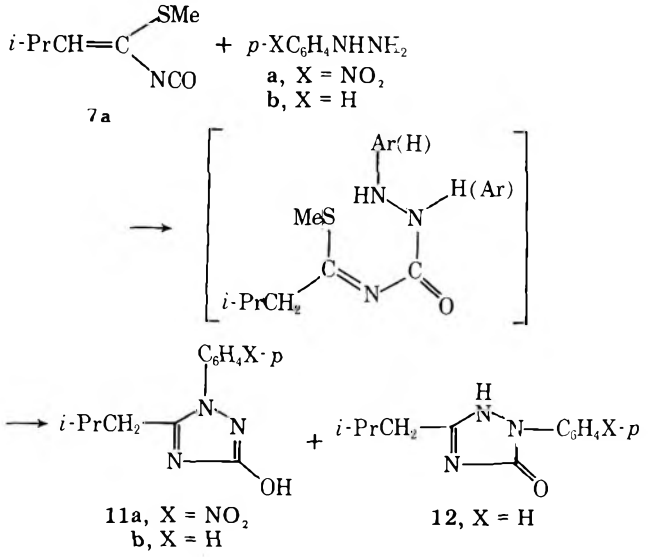
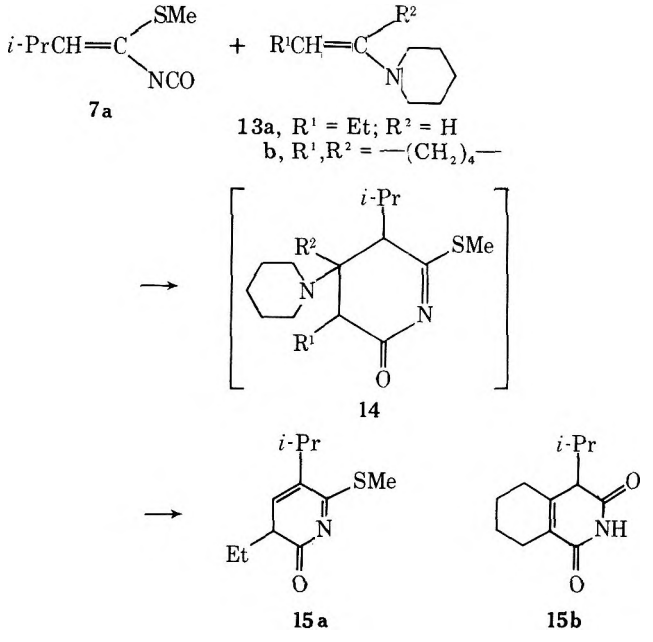
isobutyl-1,2,4-triazole (**11a**) quantitatively. With phenylhydrazine, **11b** and its isomer **12** were obtained in 57 and 43% yields, respectively. The IR spectrum of **11b** displays no absorption at the carbonyl region. The mass spectrum exhibits the parent peak at *m/e* 217 and other peaks at *m/e* 175 ($M^+ - NCO$), 106 ($PhNNH^+$), and 91 (PhN^+). On the other hand, the IR spectrum of **12** displays a strong carbonyl absorption at 1700 cm^{-1}. The mass spectrum exhibits the peak at *m/e* 119 ($PhNCO^+$) in addition to those of **11b**. On the basis of the spectral data, **11b** and **12** were assigned to 1-phenyl-3-hydroxy-5-isobutyl-1,2,4-triazole and 2-phenyl-5-isobutyl-1*H*-1,2,4-triazolin-3-one, respectively. These results suggest addition and condensation reactions of the aromatic hydrazines with the acyl isocyanate analogous to the synthesis of the triazine from the acyl isocyanate and the benzamidine.[5]

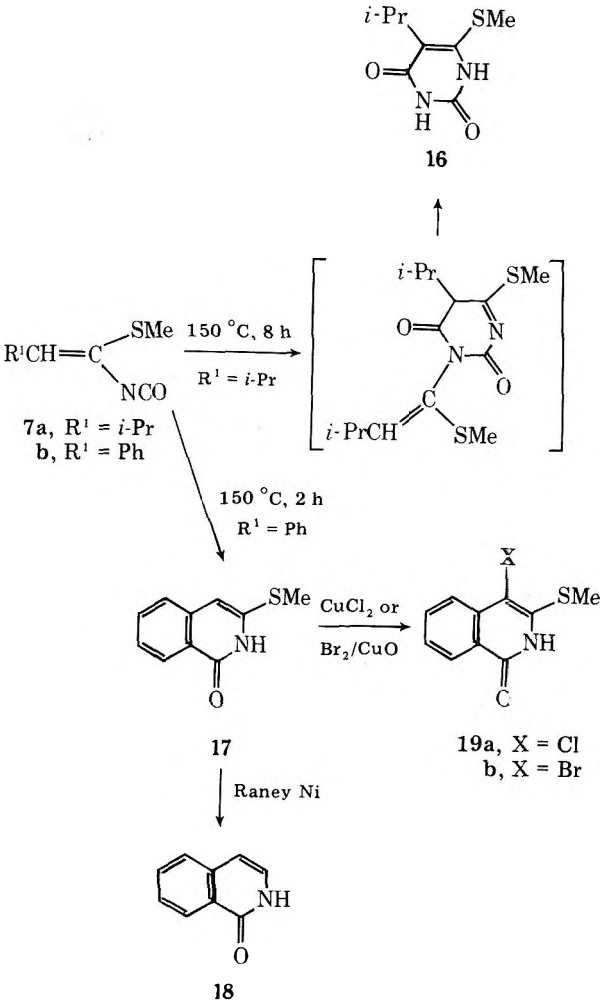


The isocyanates having a double bond adjacent to a cumulative bond are known to react with nucleophilic olefins to give 1,2- and/or 1,4-cycloadducts.[6] The reaction of **7a** with 1-piperidino-1-butene (**13a**) gave the pyridone **15a** in 69% yield. The product **15a** might be formed from **14** with elimination of the piperidine under the reaction conditions. Similar treatment of **7a** with 1-piperidino-1-cyclohexene (**13b**) led to the azadecalin derivative **15b** in 89% yield. In this case, the imino sulfide group was hydrolyzed to yield the amide group during workup in a similar way to that of **8**. Other reactions



of **7a** with dihydropyran and butyl vinyl sulfide were unsuccessful, showing lower reactivity than those of other conjugative isocyanates containing carbonyl, imidoyl and thiocarbonyl groups.

The α-alkyl(aryl)thiovinyl isocyanates **7** are stable at room temperature and remained unchanged in refluxing benzene for 15 h, while acyl isocyanates are easily decomposed under these conditions. Thermolysis of **7a** at 150 °C in neat solution gave the uracil **16** quantitatively. However, an attempt to trap other decomposition species failed; the uracil **16** was presumably formed by the dimerization reaction similar to the formation of oxadiazine derivatives from benzoyl isocyanates.[7] On the other hand, thermolysis of **7b** led to the isocarbostyril **17** quantitatively, which was easily changed to the isocarbostyril (**18**) by treatment with Raney Ni. In order to change the vinyl sulfide group to the carbonyl group, **17** was treated with $CuCl_2$–CuO in aqueous acetonitrile,[8] but the chloroisocarbostyril **19a** was obtained unexpectedly. In the absence of CuO, **19a** was not obtained and **17** was recovered. Similarly, bromination at the 4-position of **17** was achieved by the treatment with bromine in the presence of CuO. From these results, the isocyanates **7** are as useful as α-chloro- and β-



cyano-α,β-unsaturated isocyanates whose thermal treatment in the presence of hydrochloric acid also gave isocarbostyril and uracil derivatives.[4]

In conclusion, α-alkyl(aryl)thiovinyl isocyanates are prepared in good yields and are relatively stable. In the reaction with bifunctional nucleophiles such as hydrazines, the isocyanates have an equivalent value to acyl isocyanates owing to the facile elimination of the sulfide group. Furthermore, the isocyanates are applicable to the simple synthesis of uracil and isocarbostyril derivatives containing the sulfide group.

Experimental Section

General. All melting points of products were determined with a Yanagimoto micro melting point apparatus and were uncorrected. The NMR spectra were obtained on a JEOL JNM-PMX-60 and JNM-PS-100 spectrometer with tetramethylsilane as an internal standard. The IR spectra were recorded with a JASCO IRA-1 spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

Synthesis of α-Alkyl(aryl)thiovinyl Isocyanates 7. The acid chlorides **5** were prepared from the aldehydes **1** and the methyl methyl(phenyl)thioacetates **2** according to the established method.[9] The acid chloride **5a** (44.6 g, 0.25 mol) in dry ether (50 mL) was added to a stirred aqueous solution of sodium azide (23.1 g, 0.36 mol) below 5 °C, and stirring was continued at 15–20 °C until IR absorption of the acid chloride disappeared. The organic layer was extracted with ether and dried over sodium sulfate. The ethereal solution of the acyl azide **6a** was added dropwise to 150 mL of dry benzene at 70 °C, and the mixture was stirred until evolution of nitrogen gas ceased (for ~1 h). After removal of the solvent, the residue was distilled in vacuo to give 17.7 g (45%) of 1-methylthio-3-methylbut-1-enyl isocyanate (**7a**). Photolysis of the acyl azide **6b** was carried out in dry benzene at room temperature with a high-pressure mercury lamp for 10 h. **7a:** bp 34–41 °C (3 mm); IR (neat) 2240, 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 157 (M^+); NMR ($CDCl_3$) δ 1.00 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.28 (s, 3 H, SCH_3), 2.43–3.03 (m, 1 H, CH), 5.17 and 5.40 (d, *J* = 9.0 Hz, total 1 H, ratio 87:13, CH=C). α-Methylthiostyryl isocyanate (**7b**): 82% yield (thermolysis), 59% yield (photolysis); bp 78–80 °C (0.015 mm); IR (neat) 2240, 1610 cm^{-1}; mass spectrum (70 eV) *m/e* 191 (M^+); NMR ($CDCl_3$) δ 2.10 (s, 3 H, SCH_3), 5.92, and 6.28 (s, total 1 H, ratio 94:6, CH=C), 7.04–7.28 (m, 3 H, aromatic), 7.32–7.50 (m, 2 H, aromatic). 1-Phenylthio-3-methylbut-1-enyl isocyanate (**7c**): 63% yield; bp 115–120 °C (0.5 mm); IR (neat) 2240, 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 219 (M^+); NMR ($CDCl_3$) δ 1.02 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.54–3.18 (m, 1 H, CH), 5.62, and 6.53 (d, *J* = 9.4 Hz, total 1 H, ratio 75:25, CH=C), 7.12–7.66 (m, 5 H, aromatic).

Treatment of 7a with Ethanol. To the soltuion of **7a** (1.6 g, 10 mmol) in dry benzene (20 mL) was added 5 mL of absolute ethanol, and the mixture was stirred for 4 h at room temperature. After removal of the solvent, the residue was chromatographed on silica gel with hexane–benzene to give crude *N*-carboethoxy-1-methylthioisoamylideneimine (**8a**). Distillation in vacuo gave the pure sample (1.8 g, 89%). **8a:** bp 57–58 °C (1.5 mm); IR (neat) 1720, 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 203 (M^+); NMR ($CDCl_3$) δ 1.00 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 1.37 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.73–2.80 (m, 3 H), 2.37 (s, 3 H, SCH_3), 4.30 (q, *J* = 7.2 Hz, 2 H, OCH_2).

Anal. Calcd for $C_9H_{17}NO_2S$: C, 53.19; H, 8. 43; N, 6.89. Found: C, 53.01; H, 8.49; N, 6.94.

Hydrolysis of 8a. The imino sulfide **8a** (0.7 g, 3 mmol) was chromatographed on alumina with benzene–ethanol to give 3-methylbutyramide (**9a**) quantitatively: mp 134–135 °C (benzene–ethanol); IR (Nujol) 1620 cm^{-1}; mass spectrum (70 eV) *m/e* 101 (M^+); NMR ($CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 1.87–2.33 (m, 3 H), 5.83 (br, 2 H, NH_2).

Anal. Calcd for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.25; H, 11.16; N, 13.81.

Hydrolysis of 7a. The isocyanate **7a** (0.7 g, 4 mmol) was chromatographed on alumina with benzene–ethanol to give **9a** (0.35 g, 95%).

Hydrolysis of 7b. Similar treatment of **7b** (2.7 g, 14 mmol) on alumina gave 1.4 g (74%) of phenylacetoamide (**9b**): mp 165–167 °C (ethanol); IR (Nujol) 3320, 3160, 1625 cm^{-1}; mass spectrum (70 eV) *m/e* 135 (M^+); NMR (Me_2SO-d_6) δ 2.35 (s, 2 H, CH_2), 6.84 (br, 1 H, NH), 7.16–7.32 (m, 5 H, aromatic), 7.44 (br, 1 H, NH).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.14; H, 6.70; N, 10.22.

Reaction of 7b with Aniline. A mixture of **7b** (0.4 g, 2 mmol) and aniline (0.4 g, 4 mmol) in dry benzene (20 mL) was stirred for 1 h at room temperature. After removal of the solvent, the residue was chromatographed on alumina with benzene–hexane to give 0.5 g (76%) of *N*-phenyl-*N'*-phenylcarbamoylphenylacetoamidine (**10**): mp 179–180 °C (ethanol); IR (Nujol) 3220, 1700, 1650, 1575 cm^{-1}; mass spectrum (70 eV) *m/e* 329 (M^+); NMR ($CDCl_3$) δ 3.62 (s, 2 H, CH_2), 6.70–7.62 (m, 16 H, aromatic and NH), 11.96 (br, 1 H, NH).

Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.42; H, 5.68; N, 12.76.

Reaction of 7a with Aromatic Hydrazines. To the solution of **7a** (1.6 g, 10 mmol) in dry benzene (30 mL) was added *p*-nitrophenylhydrazine (1.7 g, 11 mmol) under a nitrogen atmosphere and stirring was continued for 1 h at room temperature. Crystals precipitated and were filtered to give 2.7 g (100%) of **11a**: mp 277–278 °C (methanol); IR (Nujol) 3080, 1590, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 262 (M^+); NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 1.87–2.60 (m, 1.5 H), 2.92 (d, *J* = 7.0 Hz, 2 H, CH_2), 7.66–8.00 (m, 2 H, aromatic), 8.27–8.57 (m, 2 H, aromatic).

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.95; H, 5.38; N, 21.37. Found: C, 54.85; H, 5.25; N, 21.46.

A mixture of **7a** (1.6 g, 10 mmol) and phenylhyrazine (1.1 g, 10 mmol) in dry benzene (30 mL) was stirred for 1 h at room temperature under a nitrogen atmosphere. After removal of the solvent, the residue was chromatographed on silica gel with benzene–ethanol to give **11b** and **12** in 57 (1.23 g) and 43% (0.93 g) yields, respectively.

11b: mp 194–195 °C (benzene–hexane); IR (Nujol) 1590 cm^{-1}; mass spectrum (70 eV) *m/e* 217 (M^+, 23%), 175 (M^+ − NCO, base peak), 106 ($PhNNH^+$, 11%), 91 (PhN^+, 23%); NMR ($CDCl_3$) δ 0.97 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.17 (m, 1 H, CH), 2.65 (d, *J* = 7.0 Hz, 2 H, CH_2), 7.36–7.56 (m, 5 H, aromatic), 12.53 (br, 1 H, OH).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.60; H, 7.04; N, 18.97.

12: mp 159–159.5 °C (ethanol); IR (Nujol) 1700, 1590 cm^{-1}; mass spectrum (70 eV) *m/e* 217 (M^+, 72%), 175 (M^+ − NCO, base peak), 119 ($PhNCO^+$, 6%), 91 (PhN^+, 54%); NMR ($CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.13 (m, 1 H, CH), 2.53 (d, *J* = 7.0 Hz, 2 H, CH_2), 7.20–7.67 (m, 3 H, aromatic), 7.83–8.13 (m, 2 H, aromatic), 12.10 (br, 1 H, NH).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.30; H, 6.92; N, 19.25.

Reaction of 7a with Enamines. To the solution of **7a** (1.6 g, 10 mmol) in dry benzene (20 mL) was added 1-piperidino-1-butene (**13a**) (1.4 g, 10 mmol) with stirring under a nitrogen atmosphere and the mixture was refluxed for 6 h. After removal of the solvent, the residue was chromatographed on silica gel with hexane–benzene to give 1.45 g (69%) of 3-ethyl-5-isopropyl-6-methylthio-2-pyridone (**15a**): mp 125–125.5 °C (benzene–exane); IR (Nujol) 1630, 1595, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 211 (M^+); NMR ($CDCl_3$) δ 1.00 (t, *J* = 6.0 Hz, 3 H, CH_3), 1.24 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.21–2.62 (m, 2 H, CH_2), 2.51 (s, 3 H, SCH_3), 3.09–3.57 (m, 2 H, allylic), 7.20 (d, *J* = 7.0 Hz, 1 H, vinylic).

Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.54; H, 8.11; N, 6.63; S, 15.15. Found: C, 62.55; H, 8.17; N, 6.59; S, 15.54.

After similar treatment of **7a** (1.6 g, 10 mmol) with 1-piperidino-1-cyclohexene (**13b**) (1.7 g, 10 mmol), the residue was chromatographed on alumina with hexane–benzene to give 1,3-dioxo-4-isopropyl-9,10-dehydro-2-azadecalin (**15b**) in 89% (1.85 g) yield. **15b:** mp 107.5–109 °C (ether); IR (Nujol) 3200, 3075, 1730, 1660 cm^{-1}; mass spectrum (70 eV) *m/e* 207 (M^+); NMR ($CDCl_3$) δ 1.03 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 1.66–2.63 (m, 7 H), 3.06–3.36 (m, 2 H), 4.36 (d, *J* = 8.6 Hz, 1 H, *i*-PrCH), 8.03 (br, 1 H, NH).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.42; N, 6.69.

Thermolysis of 7a. The isocyanate **7a** (0.9 g, 6 mmol) was heated in neat solution at 150 °C for 8 h and the reaction mixture was solidified after cooling. The solid was washed with ether and recrystallized from benzene–ethanol to give 0.4 g (100%) of **16**: mp 235–237 °C; IR (Nujol) 3220, 3120, 1710, 1650, 1560 cm^{-1}; mass spectrum (70 eV) *m/e* 200 (M^+); NMR (Me_2SO-d_6) δ 1.20 (d, *J* = 7.0 Hz, 6 H, 2 CH_3), 2.57 (s, 3 H, SCH_3), 3.18 (m, 1 H, CH), 10.40–11.23 (br, 2 H, 2 NH).

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.99; H, 6.04; N, 13.99; S, 15.99. Found: C, 47.95; H, 5.92; N, 13.82;, S, 16.03.

Thermolysis of 7b. The thermolysis of **7b** (1.9 g, 10 mmol) was carried out in neat solution at 150 °C for 2 h. After similar workup described above, **17** was obtained quantitatively (1.9 g). **17:** mp 170–171 °C (benzene–ethanol); IR (Nujol) 3150, 1640, 1610, 1600, 1550 cm^{-1}; mass spectrum (70 eV) *m/e* 191 (M^+); NMR ($CDCl_3$) δ 2.60 (s, 3 H, SCH_3), 6.24 (s, 1 H, vinylic), 7.20–7.66 (m, 3 H, aromatic), 8.28–8.44 (m, 1 H, aromatic), 12.04 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_9NOS$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.66; H, 4.58; N, 7.44.

Treatment of 17 with Raney Ni. A suspension of **17** (1.0 g, 5 mmol) in 30 mL of ethanol containing excess Raney Ni was refluxed for 15 h. The organic layer was separated and concentrated. Recrystallization of the residue from benzene gave 0.6 g (79%) of **18**: mp 203–205 °C (lit.[10] mp 210.5–211 °C); IR (Nujol) 3160, 1650, 1625, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 145 (M^+); NMR ($CDCl_3$) δ 6.57 (d, *J* = 7.6 Hz, 1 H), 7.13–7.73 (m, 4 H), 8.33–8.60 (m, 1 H), 11.87 (br, 1 H).

Anal. Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.41; H, 5.04; N, 9.52.

Chlorination of 17. A suspension of **17** (1.0 g, 5 mmol), $CuCl_2 \cdot 2H_2O$ (1.8 g) and CuO (1.8 g) in acetonitrile–water (25:1 mL) was refluxed

for 6 h with stirring. The mixture was filtered, extracted with ether, and dried over sodium sulfate. After concentration, 0.45 g (40%) of **19a** was obtained. **19a:** mp 217–218 °C (ethanol); IR (Nujol) 3140, 1660, 1600, 1580, 1550 cm^{-1}; mass spectrum (70 eV) *m/e* 225 (M^+); NMR (Me_2SO-d_6) δ 2.53 (s, 3 H, SCH_3), 7.37–7.87 (m, 3 H, aromatic), 8.10–8.33 (m, 1 H, aromatic), 11.63 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_8NOSCl$: C, 53.22; H, 3.55; N, 6.21; S, 14.19; Cl, 15.74. Found: C, 53.07; H, 3.40; N, 6.21; S, 14.02; Cl, 15.52.

Bromination of 17. To a suspension of 17 (0.5 g, 2.6 mmol) and CuO (0.5 g) in ethanol (30 mL) was added bromine (1 g) at room temperature and the mixture was heated at 60 °C for 7 h with stirring. After cooling, the precipitate was filtered and washed with hot ethanol. The filtrate was concentrated to give 0.7 g (100%) of **19b:** mp 220–222 °C (ethanol); IR (Nujol) 3120, 1650, 1600, 1570, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 269 (M^+); NMR ($CDCl_3$) δ 2.66 (s, 3 H, SCH_3), 7.33–7.94 (m, 3 H, aromatic), 8.12–8.36 (m, 1 H, aromatic), 11.61 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_8NOSBr$: C, 44.44; H, 2.96; N, 5.19. Found: C, 44.42; H, 2.81; N, 5.11.

Registry No.—**5a,** 64188-42-7; **5b,** 64188-40-5; **5c,** 64188-38-1; (*E*)-**6a,** 64188-36-9; (*Z*)-**6a,** 64188-34-7; (*E*)-**6b,** 64188-33-6; (*Z*)-**6b,** 64188-35-8; (*E*)-**6c,** 64188-32-5; (*Z*)-**6c,** 64188-56-3; (*E*)-**7a,** 64188-55-2; (*Z*)-**7a,** 64188-54-1; (*E*)-**7b,** 64188-53-0; (*Z*)-**7b,** 64188-52-9; (*E*)-**7c,** 64188-50-7; (*Z*)-**7c,** 64188-51-8; **8a,** 64188-49-4; **8b,** 64188-48-3; **9a,** 541-46-8; **9b,** 103-81-1; **10,** 64188-47-2; **11a,** 64188-46-1; **11b,** 64188-45-0; **12,** 28669-33-2; **13a,** 7182-10-7; **13b,** 2981-10-4; **15a,** 64188-44-9; **15b,** 64188-43-8; **16,** 64188-41-6; **17,** 64188-39-2; **18,** 491-30-5; **19a,** 64188-37-0; **19b,** 64201-56-5; aniline, 62-53-3; *p*-nitrophenylhydrazide, 100-16-3; phenylhydrazide, 100-63-0.

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Synthesis of *N*-Methyl-1-oxa-5-aza[10]paracyclophane: A Conformationally Restricted Analogue of Phenoxypropylamines[1a]

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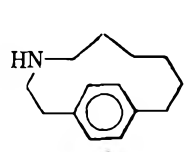
Received June 30, 1977

The synthesis of *N*-methyl-1-oxa-5-aza[10]paracyclophane (4) is reported; this represents the first example of this ring system being formed via an intramolecular halo–phenoxide reaction (ether synthesis). Attempts to synthesize phenoxyethylamine and phenoxypropylamine analogues by the acyloin reaction or by the intramolecular amine–ester reaction failed to yield the desired paracyclophanes.

Many compounds have been prepared as conformationally restricted analogues of phenethylamine in order to assess stereochemical requirements of the drug receptor.[2] These served as a stimulant for the recent publication[3] of the synthesis of 3-aza[10]paracyclophane (1) and *N*-methyl-3-aza[10]paracyclophane (2). In this paper, we are reporting the results of synthesis of conformationally restricted analogues 3 and 4 of adrenergic antagonists which contain the basic aryloxyethylamine or aryloxypropylamine structure (e.g., phenoxybenzamine and propranolol).



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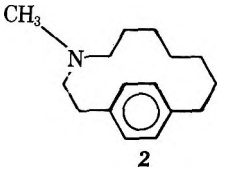

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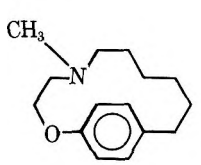

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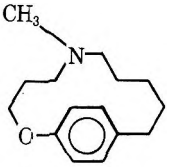
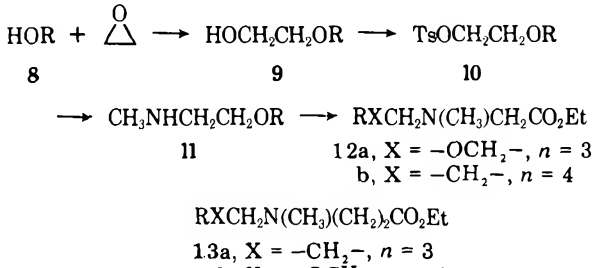


4

Since the acyloin reaction is perhaps the most important method for preparing paracyclophanes,[4] the first approach studied attempted to synthesize an oxazaparacyclophane (3) by utilizing the appropriate diester (**12a**) in an acyloin reaction (Scheme I). The diester was obtained in a straightforward manner through Friedel–Crafts acylation[5] of anisole by succinic anhydride. The keto acid **5** was reduced by the Clemmensen method,[6] and the resulting acid **6** was treated with 48% hydrobromic acid. The phenolic acid **7** was esterified[7] and the phenolic ester **8** reacted with ethylene oxide followed by tosylation and amination to give the amino ester **11**. Alkylation with ethyl bromoacetate resulted in the diester **12a.** However, under normal acyloin reaction conditions,[9] this diester failed to undergo the cyclization reaction. Only starting material and a polymeric substance were isolated from the reaction mixture.

Recently, Wu and co-workers[3b,8] found that a diester (**12b**) with an ester group one carbon length away from the nitrogen atom would not cyclize in the acyloin reaction. However, with

Scheme I[a]



8 9 10 11

12a, X = $-OCH_2-$, $n = 3$
b, X = $-CH_2-$, $n = 4$

13a, X = $-CH_2-$, $n = 3$
b, X = $-OCH_2-$, $n = 3$

[a] R = $-Ph(CH_2)nCO_2Et$, $n = 3, 4$.

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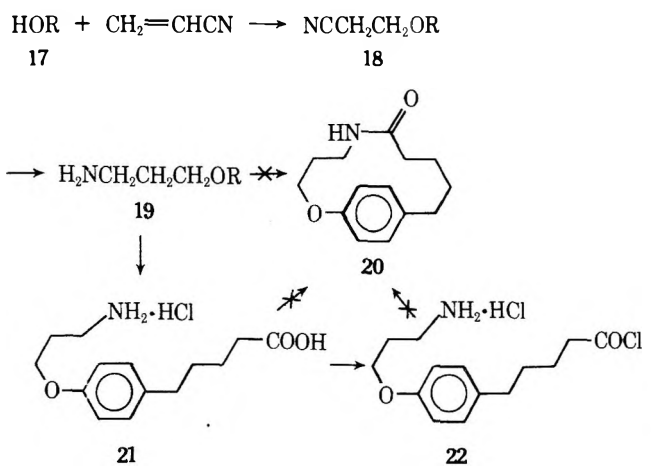
Scheme II[a]



[a] R = -Ph(CH$_2$)$_4$CO$_2$CH$_3$.

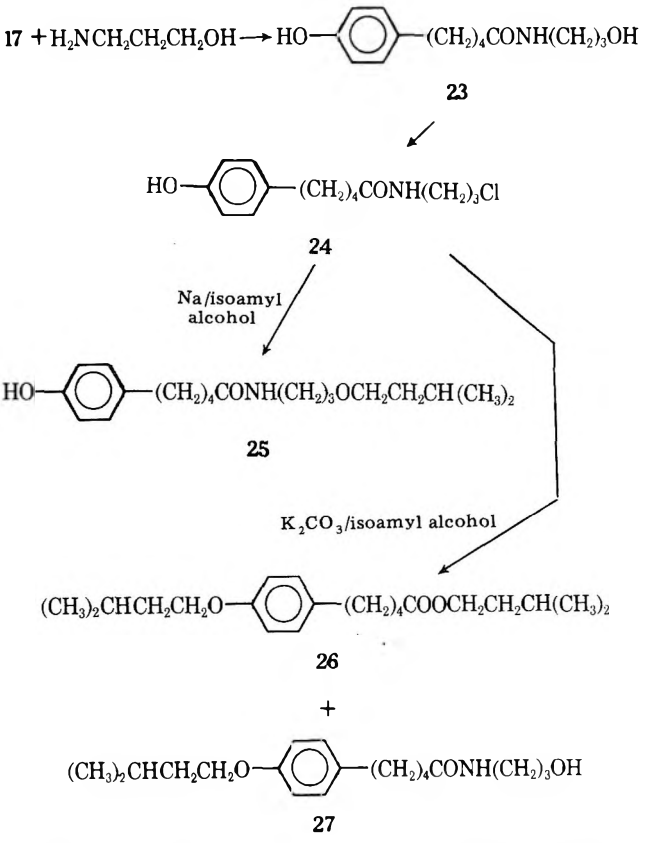
diester **13a** the acyloin reaction gave the cyclized product which was utilized to prepare the paracyclophane **2**. Replacing ethyl bromoacetate by ethyl bromopropionate (Scheme I) gave diester **13b** with the ester group two carbon lengths away from the nitrogen atom. This diester (**13b**) still failed to undergo the normal acyloin reaction. Addition of trimethylchlorosilane (Me_3ClSi)[10] to the reaction process also failed to produce any cyclized product.

Since the important acyloin reaction failed, other intramolecular reactions were considered. The second attempt involved the intramolecular amine–ester reaction (Scheme II). The synthetic route for the synthesis of **17** was similar to that described in Scheme I, except glutaric anhydride was used instead of succinic anhydride. Michael reaction of the phenolic ester **17** with acrylonitrile, followed by catalytic hydrogenation, gave the amino ester **19**. Refluxing the amino ester **19** in xylene or Dowtherm-A for 5 days gave a small amount of polymeric intermolecular amide as indicated by TLC and IR. Most of the amino ester was recovered without change. These results suggested a modification of the ester group in an attempt to obtain a more reactive moiety.

First, the ester was converted to the acid **21**. In order to facilitate reaction of the amino group with the carboxyl group, an attempt to form a mixed anhydride at the carboxylic acid moiety was studied. This was done by using dicyclohexylcarbodiimide (DCC)[11] or 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[12] as in peptide-synthesis techniques. But, due to the limited solubility of the amino acid **21** in acetonitrile or methylene chloride, the reaction was unsuccessful. Similar results were obtained when the acyl halide moiety **22** replaced the carboxylic acid group.

Finally, the intramolecular halo–ether reaction was considered for the synthesis of an oxazaparacyclophane. The phenolic halide **24** was prepared by amination of the phenolic ester **17** with 3-amino-1-propanol, followed by treatment with thionyl chloride (Scheme III). When the phenolic halide was subjected to the intramolecular halo–phenoxide reaction,[13] ether **25** was isolated in 80% yield. A possible explanation is that isoamyl alcohol reacts with sodium to form the alkoxide anion instead of the phenoxide anion, and the alkoxide anion displaced the halogen. Therefore, potassium carbonate was used to modify the reaction condition in an attempt to achieve a selective reaction with only the phenolic moiety (Scheme III). However, two products were isolated from the reaction mixture. Compound **27** was the major product (60% yield), whereas **26** was isolated in a maximum yield of only 5%. Possible explanations for the reaction products involve the presence of the amide proton on phenolic halide **24**.

Scheme III

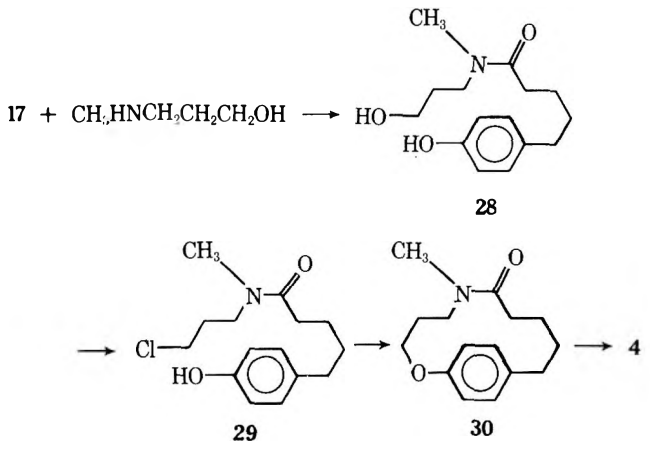


Structural assignment for compounds **25** and **27** was based on the IR and NMR spectrum and elemental analysis. Structural assignment for **26** was based on the IR and NMR spectrum only. Compound **27** gave a positive chromic anhydride test[14] and a negative bromine in water test,[14] indicating the presence of an alcoholic group and not a phenolic group.

To solve the amide proton problem, the phenolic halide **29** (Scheme IV) was prepared by amination of the phenolic ester **17** with *N*-methyl-3-amino-1-propanol, followed by treatment with thionyl chloride. When compound **29** was subjected to the high dilution intramolecular halo–phenoxide reaction, a yellowish thick oil was obtained. Chromatographic separation provided the lactam **30**. Lithium aluminum hydride reduction gave the desired product, *N*-methyl-1-oxa-5-aza[10]paracyclophane (**4**).

Structural assignments for **30** and **4** were confirmed by IR, NMR, and MS. Compound **4** gave the correct elemental analysis. The NMR spectra also provided further evidence for the paracyclophane. The open-chain phenolic alcohol **28** and

Scheme IV



phenolic halide **29** showed two methyl peaks at δ 2.89, 3.0 and δ 2.85, 3.0, respectively, representing the anti and syn conformers with the anti conformer dominating approximately 2:1. After cyclization, the lactam **30** also showed two methyl peaks at δ 2.88 and 3.0, but with equal intensity as expected. The NMR temperature-dependent studies showed these two methyl peaks coalesced at 70 °C. On cooling, the single peak separated again. This suggests that at room temperature the rotation about the central C–N bond of the disubstituted amide **30** is hindered, and two resonance peaks were observed. When the temperature was increased to 70 °C, the energy barrier about the C–N bond was overcome and coalescence occurred. The methylene protons at positions 3, 8, and 9 of compound **4** are shifted to δ 1.3 compared to 1.6 of the open-chain compounds **28** and **29**. This also suggests that protons are shielded by the aromatic ring as is the character of paracyclophanes.[15]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 467 grating spectrophotomer. The NMR spectra were determined on a Hitachi Perkin-Elmer R20 A high-resolution NMR spectrometer using tetramethylsilane (Me_4Si) as internal reference. Mass spectra were determined on a Dupont 21-490 mass spectrometer, Department of Biochemistry, University of Georgia. Elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, Georgia. TLC were performed on Eastman Chromatogram sheets, Type 6060 (silica gel).

β-Anisoylpropionic acid (**5**) was prepared from anisole and succinic anhydride, mp 145–146 °C (lit. mp 144.5–146.5 °C).[5] Reduction of **5** by the Clemmensen method[6] gave γ-(*p*-methoxyphenyl)butyric acid (**6**), mp 56–58 °C (lit. mp 56 °C).[5] The keto acid **6** was treated with 48% hydrobromic acid to yield γ-(*p*-hydroxyphenyl)butyric acid (**7**), mp 104–106 °C (lit. mp 110–111 °C).[16] γ-Anisoylbutyric acid (**14**) was prepared from anisole and glutaric anhydride, mp 137–138 °C (lit. mp 139 °C).[16] Reduction of **14**[6] gave δ-(*p*-methoxyphenyl)valeric acid (**15**), mp 111 °C (lit. mp 116 °C).[16] Treatment of **15** with hydrobromic acid gave δ-(*p*-hydroxyphenyl)valeric acid (**16**), mp 114–116 °C (lit. mp 117–119 °C).[17] These starting materials were obtained in 75–95% yield.

Ethyl γ-(*p*-Hydroxyphenyl)butyrate (8). To the solution of **7** (180 g, 1 mol) in 700 mL of absolute ethanol was added 1 mL of concentrated hydrochloric acid. The mixture was refluxed in a Soxhlet extractor filled with a 3-Å molecular sieve[7] for 12 h. Ethanol was removed in vacuo and the residue was poured into 300 mL of water and extracted with two 200-mL portions of chloroform. The chloroform layer was dried over sodium sulfate and concentrated on the rotary evaporator. The residual liquid was distilled under reduced pressure to yield 190 g (91.3%) of colorless liquid: bp 125 °C (0.005 mm); IR (neat) 3450, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, ethyl CH_3), 1.95 (m, 2 H, β-CH_2), 2.21 and 2.55 (2 t, 4 H, α- and γ-CH_2's), 4.14 (q, 2 H, ethyl CH_2), 6.8 and 7.04 (2, d, 4 H, aromatic H's), 7.41 (s, 1 H, phenol).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 68.97; H, 7.81.

Ethyl γ-[*p*-(2-Hydroxyethoxy)phenyl]butyrate (9). A mixture of **8** (4.16 g, 0.2 mol), potassium carbonate (27.6 g, 0.2 mol), and 300 mL of absolute ethanol was refluxed for 2 h. After cooling, the reaction mixture was placed in an ice–salt bath and 25 g (0.55 mol) of ethylene oxide was added. The whole mixture was warmed slowly to room temperature and stirred for 36 h under a closed system. After filtration, the alcohol was removed in vacuo to yield a highly viscous liquid (quantitative); IR (neat) 3490, 1748 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, ethyl CH_3), 1.88 (m, 2 H, β-CH_2), 2.19 and 2.56 (2 t, 4 H, α- and γ-CH_2's), 3.91 (s, 4 H, OCH_2CH_2O), 4.1 (q, 2 H, ethyl CH_2), 6.8 and 7.09 (2 d, 4 H, aromatic H's).

A phenylurethane derivative[18] of **9** was prepared: mp 82–84 °C.

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.78; H, 6.80; N, 3.77.

Ethyl γ-[*p*-(2-*p*-Toluenesulfonoxyethoxy)phenyl]butyrate (10). To a solution of **9** (50 g, 0.2 mol) in 200 mL of dry pyridine was added *p*-toluenesulfonyl chloride (38 g, 0.21 mol), at or below 0 °C, over a period of 20 min. The mixture was stirred at 0 °C for 4 h and then poured into 300 mL of cold 6 N hydrochloric acid and extracted two times with 300-mL portions of ether. After removing the ether, the crude thick liquid (70.5 g, 87%) was used without further purification: IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, 3 H, ethyl CH_3), 1.92 (m, 2 H, β-CH_2), 2.39 (s, 3 H, $ArCH_3$), 2.2–2.62 (m, 4 H, α- and γ-CH_2's), 4.1 (q, 2 H, ethyl CH_2), 4.09 and 4.32 (m, 4 H, OCH_2CH_2O), 6.68 and 7.06 (2 d, 4 H. aromatic H's), 7.3 and 7.82 (2 d, 4 H, tosyl aromatic H's).

Ethyl γ-[*p*-(2-*N*-Methylaminoethoxy)phenyl]butyrate (11). In a 1-L round-bottomed flask was placed 40.6 g (0.1 mol) of **10**, 400 mL of aqueous 40% methylamine solution, and 400 mL of chloroform. The mixture was stirred vigorously for 2 days at room temperature and poured into a separatory funnel. The chloroform layer was separated and the water layer extracted two times with 100-mL portions of chloroform. The combined chloroform layer was dried over magnesium sulfate and removed in vacuo. The residual liquid was distilled under reduced pressure to yield 13.1 g (50%) of slightly yellow liquid: bp 140 °C (0.01 mm); IR (neat) 3370, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H, ethyl CH_3), 1.9 (m, 2 H, β-CH_2), 2.4 and 2.79 (m, 4 H, α- and γ-CH_2's), 2.48 (s, 3 H, NCH_3), 3.95 (s, 1 H, NH), 4.05 (q, 2 H, ethyl CH_2), 6.8 and 7.1 (2 d, 4 H, aromatic H's).

The hydrochloride salt was prepared by dissolving **11** in ether followed by treatment with hydrogen chloride gas. The salt was collected by filtration: mp 136–138 °C.

Anal. Calcd for $C_{15}H_{23}NO_3$·HCl: C, 59.69; H, 8.02; N, 4.64; Cl, 11.75. Found: C, 59.83; H, 8.03; N, 4.78; Cl, 11.62.

Ethyl γ-[*p*-(2-*N*-Methyl-*N*-carboethoxymethylaminoethoxy)phenyl]butyrate (12a). To a solution of **11** (22 g, 0.093 mol) and dicyclohexylmethylamine (DCMA) (6.2 g, 0.083 mol) in 100 mL of benzene was added 14.4 g (0.085 mol) of ethyl bromoacetate (a precipitate was deposited within 5 min from the stirred mixture). The mixture was refluxed at 80 °C for 6 h, and the precipitate was then removed by filtration. The benzene layer was washed two times with 20 mL of water and removed in vacuo. The yellowish residual liquid was distilled under reduced pressure to yield 23.5 g (80.6%) of diester: bp 180–182 °C (0.075 mm); IR (neat) 2900, 2905, 1750, 1255, 830 cm^{-1}; NMR ($CDCl_3$) δ 1.22 and 1.24 (2 t, 6 H, ethyl CH_3's), 1.88 (m, 2 H, β-CH_2), 2.5 (s, 3 H, NCH_3), 2.25 and 2.58 (m, 4 H, α- and γ-CH_2's), 3.4 (s, 2 H, NCH_2COO), 4.06 (t, 2 H, $ArOCH_2$), 4.09 and 4.11 (2 q, 4 H, ethyl CH_2's), 6.82 and 7.1 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.31; N, 3.98. Found: C, 64.80; H, 8.35; N, 3.92.

Ethyl γ-[*p*-(2-*N*-Methyl-*N*-β-carboethoxyethylaminoethoxy)phenyl]butyrate (13b). This compound was prepared by the same procedure as compound **12a**. The only difference was the use of ethyl bromopropionate instead of ethyl bromoacetate. A light yellow liquid was obtained in 75–80% yield: bp 208–210 °C (0.02 mm); IR (neat) 2940, 2860, 2800, 1730, 1612, 825 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 6 H, ethyl CH_3's), 2.36 (s, 3 H, NCH_3), 1.95–2.8 (m, 12 H, all CH_2's except $ArOCH_2$), 4.05 (t, 2 H, $ArOCH_2$), 4.1 (q, 4 H, ethyl CH_2's), 6.8 and 7.11 (2 d, 4 H. aromatic H's).

Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.49; H, 8.61; N, 3.88.

Methyl δ-(*p*-Hydroxyphenyl)valerate (17). This compound was prepared (91%) in the same manner as compound **8**, except methanol was used instead of ethanol: mp 38 °C; bp 155 °C (0.025 mm); IR (neat) 3400, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (m, 4 H, β- and γ-CH_2's), 2.4 (m, 4 H, α- and δ-CH_2's), 3.65 (s, 3 H, CH_3), 6.85 and 7.0 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.16; H, 7.77.

Methyl δ-[*p*-(2-Cyanoethoxy)phenyl]valerate (18). In a 50-mL round-bottomed flask were placed **17** (5.2 g, 0.025 mol) and a small piece of sodium metal in 30 mL of benzene. The mixture was refluxed for 3 h. After cooling to room temperature, 2.5 g, (0.05 mol) of acrylonitrile was added dropwise and the mixture refluxed for 10 h. The reaction mixture was poured carefully into 50 mL of cold 3 N hydrochloric acid and extracted with two 50-mL portions of ether. The ether layer was dried over magnesium sulfate and removed in vacuo to yield a slightly yellow oil (4.2 g, 64%). The crude product was used directly for catalytic hydrogenation without further purification: TLC ($CHCl_3$), R_f 0.45; IR (neat) 2255, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (m, 4 H, β- and γ-CH_2's), 2.0–2.5 (m, 6 H, α- and δ-CH_2's and CH_2CN), 3.6 (s, 3 H, CH_3), 3.9 (t, 2 H, $ArOCH_2$), 6.75 and 7.03 (2 d, 4 H, aromatic H's).

Methyl δ-[*p*-(3-Aminopropyloxy)phenyl]valerate Hydrochloride (19). A mixture of **18** (5.25 g, 0.025 mol), 10 mL of concentrated hydrochloric acid, 1 g of 10% palladium-on-carbon, and 250 mL of methanol was subjected to hydrogenation on a Parr apparatus; initial pressure was 53 psi. After shaking for 2 h, the pressure had dropped to 51 psi and remained constant thereafter. The solution was filtered and the methanol removed in vacuo. The crude product (3.8 g, 66%) was washed several times with ether to yield a white powder

(50%): mp 161–163 °C, TLC ($CHCl_3$), R_f 0.15; IR (KBr) 1740 cm^{-1}; NMR (Me_2SO-d_6) δ 1.5–2.5 (m, 10 H, α-, β-, γ-, and δ-CH_2's and $NCCH_2C$), 2.95 (t, 2 H, NCH_2), 3.58 (s, 3 H, CH_3), 4.02 (t, 2 H, $ArOCH_2$), 6.86 and 7.12 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{15}H_{23}NO_3$·HCl: C, 59.69; H, 8.02; N, 4.64; Cl, 11.75. Found: C, 59.52; H, 8.05; N, 4.70; Cl, 11.86.

δ-[p-(3-Aminopropyloxy)phenyl]valeric Acid Hydrochloride (21). A mixture of **19** (18 g, 0.06 mol) in 150 mL of 6 N hydrochloric acid was refluxed for 12 h. After cooling, the product was collected by filtration and recrystallized from water (14 g, 81.4%): mp 184–187 °C; IR (KBr) 1700 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_3$·HCl: C, 58.43; H, 7.71; N, 4.87; Cl, 12.32. Found: C, 58.54; H, 7.77; N, 4.82; Cl, 12.22.

δ-[p-(3-Aminopropyloxy)phenyl]valeryl Chloride Hydrochloride (22). To a mixture of **21** (10 g, 0.037 mol) in 50 mL of benzene was added 4.2 g (0.04 mol) of thionyl chloride. The reaction mixture was refluxed for 1 h. After cooling, the crude product was filtered. However, the acyl chloride was unstable and hydrolyzed to the corresponding acid within 2 h: mp 144–146 °C; IR (KBr) 1815 cm^{-1}.

***N*-(3-Hydroxypropyl)-δ-(*p*-hydroxyphenyl)valeramide (23).** A mixture of phenolic ester **17** (20.8 g, 0.1 mol) and 3-amino-1-propanol (15 g, 0.2 mol) was placed in a 200-mL round-bottomed flask and heated at 130 °C for 10 h. Approximately 3 mL of methanol was collected in a Dean–Stark apparatus. The excess 3-amino-1-propanol was removed by distillation under reduced pressure to yield quantitatively a dark-brown thick oil, which decomposed on micromolecular distillation. Without further purification, compound **23** was converted to the corresponding alkyl halide **24** in the following reaction: TLC (chloroform/acetone) R_f 0.2; IR (neat) 3300, 1640 cm^{-1}; NMR (pyridine-d_5) δ 1.5–1.9 (m, 6 H, β- and γ-CH_2's and $NCCH_2C$), 2.1–2.48 (m, 4 H, α- and δ-CH_2's), 3.45 (t, 2 H, NCH_2), 3.72 (t, 2 H, CH_2O), 7.0 (s, 4 H, aromatic H's).

***N*-(3-Chloropropyl)-δ-(*p*-hydroxyphenyl)valeramide (24).** In the same flask of the above reaction, compound **23** was placed in an ice–salt bath. Thionyl chloride (25 mL) was added dropwise over a period of 1 h. After warming to room temperature, stirring was started and continued overnight. The reaction mixture was poured into 300 mL of ice water and extracted with two 200-mL portions of methylene chloride. The methylene chloride extract was then passed through a silica gel column, using the same solvent as eluent, to yield a yellow thick liquid (13 g, 48.3%): TLC (chloroform/acetone) R_f 0.6; IR (neat) 3300, 1630 cm^{-1}; NMR (acetone-d_6) δ 1.59–2.49 (m, 10 H, α-, β-, γ-, and δ-CH_2's and $NCCH_2C$), 3.37 (t, 2 H, NCH_2), 3.57 (t, 2 H, CH_2Cl), 6.7 and 6.97 (2 d, 4 H, aromatic H's), 7.5 (s, 1 H, phenol); mass spectrum *m/e* 269 (M^+, calcd 269).

Anal. Calcd for $C_{14}H_{20}NO_2Cl$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.58; H, 7.55; N, 5.12; Cl, 13.02.

***N*-(3-Isoamyloxypropyl)-δ-(*p*-hydroxyphenyl)valeramide (25).** All glassware was dried overnight in an oven (ca. 150 °C) before use. A 3-L Morton flask was fitted with high-dilution apparatus[19] and a high-speed stirrer[20] with a constant flow of dry nitrogen.[21] Isoamyl alcohol[23] (1.6 L) was charged into the Morton flask and distilled into the high-dilution flask (ca. 0.8 L). Freshly cut sodium metal (6.4 g, 0.28 mol) was transferred and stirred (ca. 10 000 rpm) to make a fine suspension. The phenolic halide **24** (18.7 g, 0.07 mol) in 300 mL of isoamyl alcohol was added dropwise over a period of 10 h to the stirring (ca. 9000 rpm) and refluxing sodium suspension. After the addition was completed, refluxing was continued for 1 h and then the mixture was cooled in an ice–water bath. Acetic acid (10 mL) was added dropwise with moderate stirring, followed by 500 mL of water (under nitrogen flow). Isoamyl alcohol was separated, dried over sodium sulfate, and then removed in vacuo. The residue was purified by silica gel column chromatography, using ether as eluent, to yield a slightly yellow thick oil (17.8 g, 80%): IR (neat) 3320, 2950, 2870, 1650, 1100, 820 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 6.0 Hz, isopropyl CH_3's), 1.36–2.6 (m, 13 H, α-, β-, γ-, and δ-CH_2's, CH, and $NCCH_2COCCH_2C$), 3.25–3.55 (m, 6 H, $NCH_2CCH_2OCH_2$), 6.78 and 7.02 (2 d, 4 H, aromatic H's), 8.71 (s, 1 H, phenol).

Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 70.36; H, 9.02; N, 3.94.

A phenylurethane derivative[18] of **25** was prepared: mp 99–102 °C.

Anal. Calcd for $C_{26}H_{36}N_2O_4$: C, 70.88; H, 8.24; N, 6.36. Found: C, 70.75; H, 8.25; N, 6.37.

Isoamyl δ-(*p*-Isoamyloxyphenyl)valerate (26) and *N*-(3-Hydroxypropyl)-δ-(*p*-isoamyloxyphenyl)valeramide (27). The procedure employed for the preparation of compound **25** was used, except potassium carbonate (4 equiv) was employed as the base. The crude product was purified by chromatography on a silica gel column: Fraction 1, petroleum ether eluate, contained silicon or grease; fraction 2, chloroform eluate, gave compound **26** (5%); fraction 3, acetone eluate, gave compound **27** (60%).

Compound **26**: IR (neat) 2960, 2870, 1742, 1240, 815 cm^{-1}; NMR ($CDCl_3$) δ 0.92 and 0.96 (2 d, 12 H, J = 6.0 Hz, isopropyl CH_3's), 1.56–2.57 (m, 14 H, CH and all CH_2's except $ArOCH_2$ and $COOCH_2$), 3.97 and 4.1 (2 t, 4 H, $ArOCH_2$ and $COOCH_2$), 6.8 and 7.1 (2 d, 4 H, aromatic H's).

Compound **27**: mp 55–56 °C; IR (KBr) 3300, 2920, 1635, 1240, 800 cm^{-1}; NMR (acetone-d_6) δ 0.95 (d, 6 H, J = 6.0 Hz, isopropyl CH_3's), 1.55–2.53 (m, 13 H, CH and all CH_2's except $ArOCH_2$ and NCH_2CCH_2O), 3.25 (t, 2 H, NCH_2), 3.95 (t, 2 H, $ArOCH_2$), 6.8 and 7.1 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99, H, 9.72; N, 4.36. Found: C, 70.72; H, 9.72; N, 4.32.

***N*-Methyl-*N*-(3-hydroxypropyl)-δ-(*p*-hydroxyphenyl)valeramide (28).** The procedure described for preparing compound **23** was employed, except that *N*-methyl-3-amino-1-propanol was used instead of 3-amino-1-propanol. The crude thick oil product (quantitative yield) decomposed on micromolecular distillation. Compound **28** was converted to the halide **29** without further purification: IR (neat) 3280, 2935, 1618, 1050, 818 cm^{-1}; NMR (acetone-d_6) δ 1.7 (m, 6 H, β- and γ-CH_2's and $NCCH_2C$), 2.45 (m, 4 H, α- and δ-CH_2's), 2.89 and 3.0 (2 s, 3 H, NCH_3), 3.45 (t, 2 H, NCH_2), 3.5 (t, 2 H, CH_2O), 6.76 and 7.04 (2 d, 4 H, aromatic H's).

***N*-Methyl-*N*-(3-chloropropyl)-δ-(*p*-hydroxyphenyl)valeramide (29).** The procedure described for preparing compound **24** was used. The crude product (40%) was purified by silica gel column chromatography using methylene chloride as eluent to yield a thick brown oil (30%): IR (neat) 3220, 2920, 1605, 1225, 818, 635 cm^{-1}; NMR (acetone-d_6) δ 1.6 (m, 6 H, β- and γ-CH_2's and $NCCH_2C$), 2.4 (m, 4 H, α- and δ-CH_2's), 2.85 and 3.0 (2 s, 3 H, NCH_3), 3.45 (t, 2 H, NCH_2), 3.55 (t, 2 H, CH_2Cl), 6.76 and 7.0 (2 d, 4 H, aromatic H's).

A phenylurethane derivative[18] of **29** was prepared: mp 126 °C.

Anal. Calcd for $C_{22}H_{27}N_2O_3Cl$: C, 65.58; H, 6.76; N, 6.95; Cl, 8.80. Found: C, 65.40; H, 6.78; N, 7.00; Cl, 8.84.

***N*-Methyl-6-keto-1-oxa-5-aza[10]paracyclophane (30).** This compound was prepared in the same general setup as compound **25** above. Xylene[24] (1.6 L) was charged into the Morton flask and distilled into the high-dilution flask (ca. 0.8 L). Freshly cut sodium metal (4 g, 0.17 mol) was transferred and stirred (ca. 10 000 rpm) to make a fine suspension. The phenolic halide **29** (13.1 g, 0.046 mol) in 500 mL of xylene was added dropwise over a period of 12 h to the stirring and refluxing sodium suspension. After the addition was completed, refluxing was continued for another hour and then the mixture was cooled in an ice bath. Acetic acid (10 mL) was added dropwise with moderate stirring, followed by 500 mL of water. The xylene layer was separated from a separatory funnel. The aqueous layer was basified by sodium hydroxide (ca. pH 8.5) and extracted with two 300-mL portions of chloroform. The combined xylene and chloroform layers were dried over sodium sulfate and concentrated on the rotary evaporator to yield a gummy material. This residual product was transferred to a silica gel column. Fractions 1 and 2, methylene chloride eluate, contained grease and some unknown open-chain material. Fraction 3, acetone eluate, gave the lactam **30** (1.5 g, 20%). Fraction 4, methanol eluate, gave an unidentified polymeric material (ca. 50%). The product from fraction 3 (paracyclophane, **30**) decomposed on micromolecular distillation.[25] Therefore, compound **30** was used in the following reaction directly: IR (neat) 2923, 2850, 1630, 1240, 1050, 820 cm^{-1}; NMR (acetone-d_6) δ 1.61 (m, 6 H, $C_{3,8,9}$ CH_2's), 2.4 (m, 4 H, $C_{7,10}$ CH_2's), 2.88 and 3.0 (2 s, 3 H, NCH_3), 3.51 (t, 2 H, C_4 CH_2), 3.94 (t, 2 H, C_2 CH_2), 6.8–7.1 (m, 4 H, aromatic H's); mass spectrum *m/e* 247 (M^+, calcd 247).

***N*-Methyl-1-oxa-5-aza[10]paracyclophane (4).** In a 100-mL three-necked round-bottomed flask was placed lithium aluminum hydride (150 mg, 3.94 mmol) and 50 mL of THF[26] under a constant flow of nitrogen. Lactam **30** (350 mg, 1.41 mmol) in 30 mL of THF was added to the mixture. The reaction mixture was refluxed for 8 h and then cooled in an ice bath. Excess reagent was decomposed by slow addition of 2 mL of water in 20 mL of THF followed by 0.5 mL of 10% sodium hydroxide solution. The mixture was filtered to remove the inorganic material and the filtrate was evaporated in vacuo. The residue was passed through a silica gel column, using ether as eluent. The ether gave a crude product (100 mg, 30%) which was recrystallized from acetone to yield a white powder (65 mg): mp 125–126 °C; IR (KBr) 2920, 2795, 1510, 1240, 805 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (m, 6 H, $C_{3,8,9}$ CH_2's), 2.2 (s, 3 H, NCH_3), 2.3 (m, 4 H, $C_{7,10}$ CH_2's), 2.45 (m, 4 H, $C_{4,6}$ CH_2's), 3.99 (t, 2 H, C_2 CH_2), 6.72 and 6.96 (2 d, 4 H, aromatic H's); mass spectrum *m/e* 233 (M^+, calcd 233).

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.93; N, 5.99. Found: C, 76.99; H, 9.94; N, 5.98.

Registry No.—**4**, 64201-22-5; **6**, 4521-28-2; **7**, 7021-11-6; **8**, 62889-58-1; **9**, 64201-23-6; **9** phenylurethane, 64201-24-7; **10**, 64201-25-8; **11**, 64201-26-9; **11** HCl, 64201-27-0; **12a**, 64201-28-1; **13b**, 64201-29-2; **17**, 64201-30-5; **18**, 64201-31-6; **19**, 64201-32-7; **21**, 64201-33-8; **22**, 64201-34-9; **23**, 64201-35-0; **24**, 64201-36-1; **25**, 64201-37-2; **25** phenylurethane, 64201-38-3; **26**, 64201-39-4; **27**, 64201-40-7; **28**, 64201-41-8; **29**, 64201-42-9; **29** phenylurethane, 64201-43-0; **30**, 64201-44-1; ethylene oxide, 75-21-8; *p*-toluenesulfonyl chloride, 98-59-9; ethyl bromoacetate, 105-36-2; ethyl bromopropionate, 539-74-2; acrylonitrile, 107-13-1; 3-amino-1-propanol, 156-87-6; isoamyl alcohol, 123-51-3; *N*-methyl-3-amino-1-propanol, 42055-15-2; xylene, 1330-20-7.

References and Notes

(1) (a) Presented at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, Abstract ORGN 14; (b) Taken in part from the thesis submitted by C. S. Yi to the Graduate School of the University of Georgia in partial fulfillment of the requirements for the Ph.D. degree, May, 1977; (c) Present address: School of Pharmacy, Creighton University, Omaha, Nebraska 68178.
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(21) Dry, oxygen-free nitrogen was obtained by passing through a column of drierite and then bubbling through a solution of benzophenone ketyl in xylene which was prepared from benzophenone and a sodium potassium alloy.[22]
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(23) Isoamyl alcohol was distilled from anhydrous calcium chloride, bp 128–129 °C.
(24) Xylene was refluxed with sodium overnight and then distilled, bp 138–140 °C.
(25) Compound **30** taken directly from the column did not give acceptable elemental analysis: Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.00; H, 8.76; N, 5.03.
(26) Tetrahydrofuran was distilled from LAH, bp 68 °C.

Chemistry of Heterocyclic Compounds. 26. Synthesis and Reactions of Multiheteromacrocycles Possessing 2,6-Pyrazino Subunits Connected by Carbon–Oxygen and/or –Sulfur Linkages[1]

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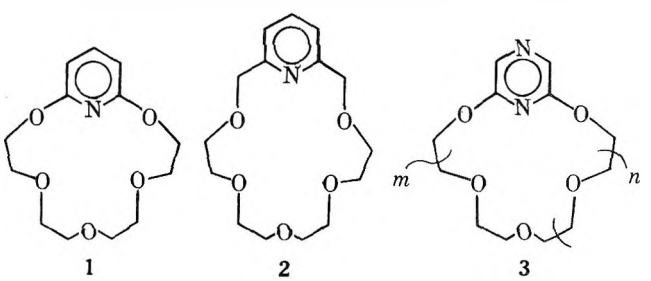
Received June 24, 1977

2,6-Dichloropyrazine (4) was treated with numerous glycol dianions, as well as the dianions of bis(2-mercaptoethyl) sulfide and bis(2-mercaptoethyl) ether, affording in most cases heteromacrocyclic ethers. Various expected uncyclized products were isolated and characterized. Quaternization of the N-4 position of the pyrazine ring was exclusively realized with these macrocycles. Diquaterization was accomplished with the 2:2-macrocycle 11, and a new series of 1,3,5-cyclophanes (e.g., 40) was generated from 5.

Recently we described the preparation and characterization of carbon–oxygen bridged 2,6-pyridino macrocycles in which the bridging oxygens are directly attached to the pyridine nucleus (e.g., 1).[2] This class of macrocycle[3] resulted from direct nucleophilic substitution of a ring halide by an alkoxide fragment and differs structurally and chemically from the macrocyclic class which possess a methylene group between the bridged heteroatoms and subring (e.g., 2).[4] We herein describe the application of this procedure to the incorporation of the 2,6-pyrazino subunit into a "crown ether" (3) and the chemistry of these difunctional subheterocyclic rings.



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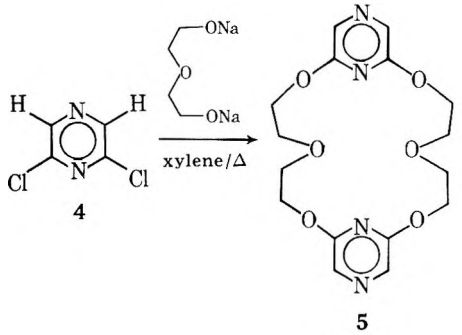
In light of potential pharmaceutical and pesticidal interest in substituted pyrazines, numerous nonmacrocyclic 2,6-disubstituted pyrazines have been synthesized from the readily available 2,6-dihalopyrazine by nucleophilic substitution. Conditions for substitution of the 2- (or 6-) halides from 2,6-dihalopyrazines by alkoxide,[5] hydroxide,[5b–d] cyanide,[5b] amines,[5b,h,l,6] alkylsulfides,[5c,7] phenoxide,[8] sulfanilamide,[5g,9] alkyl,[10] and aryl[10] have been described. Based on the above chemical substitution studies and the π-electron density calculations in the pyrazine ring,[11] 2,6-dinucleophilic substitution on the pyrazine ring should be equally, or slightly more, facile to that of our previously studied pyridine cases.[2] Although the literature contains several examples of 1,2- and 1,3-diazine subunits incorporated into macrocyclic rings, prepared also by different procedures,[3] there are, to the best of our knowledge, no examples of the 2,6-pyrazino moiety incorporated in a "crown ether" ring.[12]

A. Pyrazine Macrocycles with Carbon–Oxygen Bridges. 1. Diethylene Glycol. Reaction of 2,6-dichloropyrazine (4) with diethylene glycol dianion, generated in situ from diethylene glycol and 2 equiv of oil-free sodium hydride,

0022-3263/78/1943-0409$01.00/0

affords the 2:2- and 3:3-macrocycles (**5** and **6**, respectively) as well as the larger 40-membered 4:4-macrocycle **7**, which was isolated with difficulty. Although the smallest member (**8**) of this series was not isolated, it was not expected in view of the bridge size (ten-membered ring) and the general method of preparation. Only when the bridge possesses sulfur atoms which possess larger radii and diminished bond angle can such a ten-membered 1:1 macrocycle be generated, thus far, by this procedure; similar results have also been obtained in the related pyridine series.[2]

The spectral data for **5**–**7** were virtually superimposable; however, the ring sizes were ascertained by both mass spectrometry and molecular weight determination, and the symmetrical macrocyclic structures were confirmed by their NMR patterns. In **5**, the 3,5-pyrazine hydrogens show up as a spike at δ 7.8, a downfield shift when compared with the 3,5-pyridine hydrogens, as in **1**, which appear as a doublet at δ 6.2–6.3. This comparative downfield shift of the pyrazine proton signal is caused by the second ring nitrogen at the 4 position. Since substituents on the pyrazine ring cause pronounced and in most cases predictable shifts in the chemical shifts, care must be taken in peak assignments. For example, in the uncyclized products, such as **9**, the 3- and 5-pyrazine hydrogens appear



4

5

+

6, n = 1
7, n = 2

8

9

as a *singlet* at δ 8.15. This further downfield shift was always experienced in the uncyclized pyrazine products. The macrocyclic bridging methylene groups are readily characterized by NMR in that the $-OCH_2CH_2O-$ units appear as triplets [α: δ 4.4–4.6; β: δ 3.8–3.9; γ: δ 3.5–3.7 (a singlet with an odd number of units); δ-ω: δ 3.4–3.6 (not defined)].

2. Triethylene Glycol. When 2,6-dichloropyrazine (**4**) was reacted with triethylene glycol dianion in refluxing xylene, besides the expected 1:1 and 2:2 macrocycles (**10** and **11**, respectively), a noncyclized product **12** was obtained in good yield. **12** could be converted into **11** upon treatment with additional dianion. The structures of these products were easily confirmed by ^{1}H NMR spectroscopy. In the macrocycles the 3,5-pyrazine hydrogens appeared as a singlet at δ 7.7–7.8; whereas, in **12** the pyrazine hydrogens appeared as two sepa-

10, n = 1
13, n = 2
17, n = 3
19, n = 4

12, n = 1
15, n = 2

11, $m = n$ = 1
14, $m = n$ = 2
16, m = 1; n = 2
18, $m = n$ = 3
20, $m = n$ = 4

rate singlets: δ 8.05 to H-3 and δ 8.10 to H-5 are the tentative assignments based on later examples. Numerous other products were obtained and upon cursory NMR analysis were shown to be minor noncyclized components; further characterizations of these compounds were not conducted.

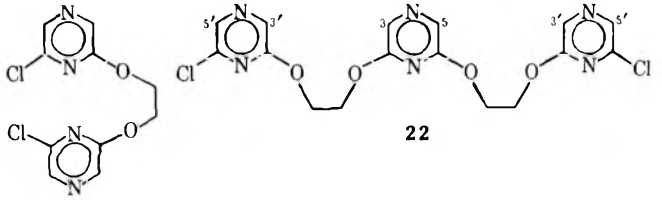
3. Tetra-, Penta-, and Hexaethylene Glycols. Reaction of the dianion of the commercially available tetraethylene glycol with **4** furnished the desired 1:1- and 2:2-macrocycles (**13** and **14**, respectively). The noncyclized products (e.g., **15**) were detected but not isolated; however, unlike our previous observation in the pyridine series,[2b] macrocycle **16** was not even detected in the reaction mixture. Prolonged reaction times caused a minor increase in the formation of the macrocyclic products.

Penta- and hexaethylene glycols were synthesized according to the procedure of Perry and Hibbert[13] by reacting ethylene glycol with 1,8-dichloro-3,6-dioxaoctane and 1,11-dichloro-3,6,9-trioxaundecane, respectively. The disodium salt of pentaethylene glycol was reacted with **4** to afford the expected 1:1 and 2:2 macrocycles as crystalline solids. Since polyglycols undergo both fragmentation as well as to a lesser extent oligomerization at reaction temperatures,[14] a 1% yield of the smaller 1:1 macrocycle **13** was realized. Similarly, hexaethylene glycolate fragmented under the reaction conditions to generate dianions which were the sources of both **10** and **13**. Macrocycles **19** and **20** were isolated from the later experiments in 15 and 2% isolated yields, respectively. In both the pyrazine as well as pyridine[2] studies, the 1:1 macrocycles derived from hexaethylene was obtained in unusually high yields

as compared with other reactions in these series, thus indicative of a possible template effect.[15]

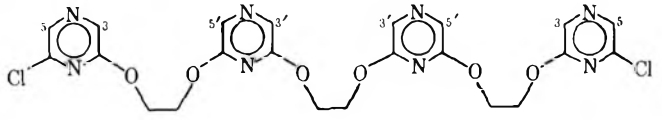
4. Ethylene Glycol. Recently, Allison et al.[5j] treated the very reactive tetrafluoropyrazine with sodioglycolate at −15 °C for 30 min; only the 1:1 and 1:2 noncyclized products were obtained. Subsequent treatment of this 1:1 adduct, 1,3,5-trifluoro-6-(2′-hydroxyethoxy)pyrazine, with either potassium *tert*-butoxide at 20 °C or potassium carbonate in dimethylformamide at 120 °C afforded a polymeric material, which was assigned[5j] as poly[2,3-bis(ethylenedioxy)-5,6-difluoropyrazine].

Treatment of 2,6-dichloropyrazine with sodioglycolate in xylene at 140 °C gave six different noncyclized products (**9**, **21–25**). Cyclic products were neither isolated nor detected from our procedures. Several attempts to prepare cyclic compounds from either **21**, **22**, or **23** by reaction with sodium glycolate failed. When lithium hydride was used as the base, there were only minor changes in product distribution. If macrocyclic products were formed, they were generated in less than 1% of the product mixture. This lack of cyclic components, so evident in the ethylene glycol series, indicates that the heteroatoms must not be capable of attaining the proper disposition of metal ion coordination (template effect). Although the NMR spectra of **21** and **9** are quite simple, the spike at δ 8.15 for the 3,5-protons is indicative of a 2-oxy-6-chloropyrazine substitution pattern. Compounds **22–25**,



21

22



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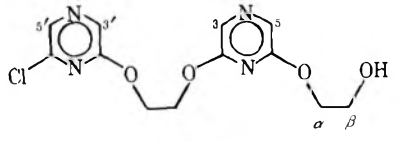

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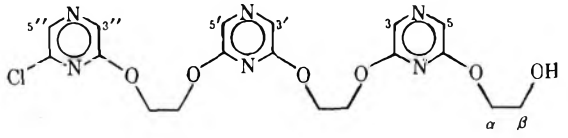
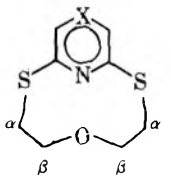


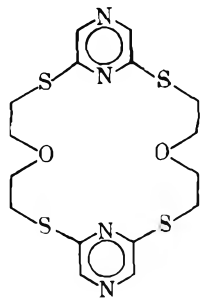
25

however, possess both a singlet at δ 8.15 for the terminal pyrazine hydrogens and a second singlet at ca. 7.8 for the internal pyrazine ring(s).

B. Pyrazine Macrocycles with Carbon–Oxygen–Sulfur Bridges. Bis(2-mercaptoethyl) Ether. Oxygen–sulfur mixed bridged macrocycles **26a** and **27** were isolated in good yield by reacting the disodium salt of bis(2-mercaptoethyl) ether with **4** in refluxing xylene. In both the pyrazine as well as pyridine series,[16] **26a** and **26b**, respectively, were the smallest isolable macrocycles possessing the corresponding subunit. The ^{1}H NMR of **26a** showed a characteristic singlet at δ 8.2 for the pyrazine ring with 2,6-disulfur substitution and triplets at δ 3.25 and 3.91 corresponding to the β- and α-methylene groups, respectively. The sulfur functionality along with the "folded-under" conformation of the bridge in **26a** resulted in a slight upfield shift of the methylene absorptions. Macrocycle **27** showed the standard spike at δ 8.1 for the



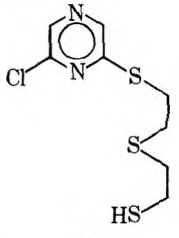
26a, X = N
b, X = CH



27

pyrazine hydrogens; however, the methylene groups appear as a complex multiplet centered at δ 3.5. This lack of differentiation of bridged methylenes was also experienced in the larger pyridine macrocycles which have sulfur atoms in the bridge(s).[16]

C. Attempted Preparation of Pyrazine Macrocycles with Carbon–Sulfur Bridges. 1. Bis(2-mercaptoethyl) Sulfide. When the disodium salt of bis(2-mercaptoethyl) sulfide was reacted with **4**, only three major components were isolated. The expected macrocycles in this carbon–sulfur series, such as **31**, were not detected; however, the noncyclic 1:1 product **28** was the key component and the remaining noncyclic products **29** and **30** were derived either from **28** or oli-



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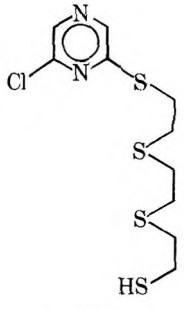

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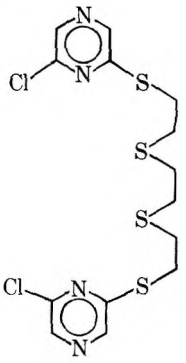

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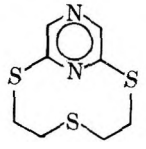
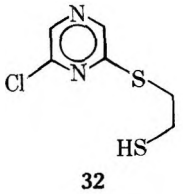


31

gomers of the bis(2-mercaptoethyl) sulfide. The noncyclic nature of **28–30** was easily ascertained by NMR data, which showed two singlets at δ 8.2 and 8.3 for the H-3 and H-5 pyrazine hydrogens. The methylene region of these sulfur-containing side chains was too complex for interpretation.

2. Ethanedithiol. Reaction of **4** with the disodio salt of ethanedithiol afforded only two major crystalline components which were shown to be 1:1 and 2:1 noncyclic compounds **32** and **33** via their NMR spectra. Attempted further cyclization of **32** was unsuccessful.



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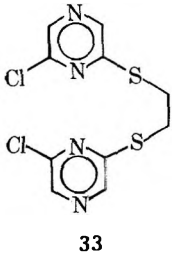
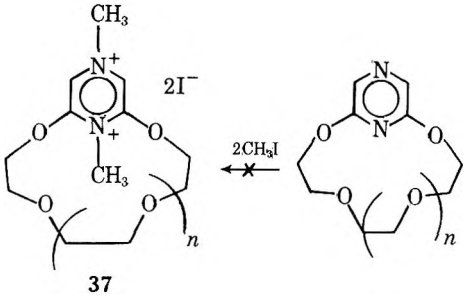


33

In general, the dithiols appear to undergo facile oligomerization prior to nucleophilic ring attack. Similar results were experienced in the preparation of pyridine–sulfur bridged macrocycles.[16] Further work in the carbon–sulfur bridged pyrazine-containing macrocycles was abandoned due to lack of isolable cyclic products and the general properties of the reactants.

D. Quaternization of Selected Pyrazine Macrocycles. A Route to Cyclophanes. From a limited number of literature examples of substituted pyrazine quaternization,[17] it appears that 2- (or 2,6-) substitution patterns give rise to N-4 alkylation as the major product. When the 1:1 carbon–oxygen bridged pyrazines were heated with excess methyl iodide, the N-4 methiodides (**34–36**) were obtained in near quantitative yields. Attempted further N-alkylation at the remaining N-1 position, to generate **37**, was unsuccessful. Similarly, the 1:1



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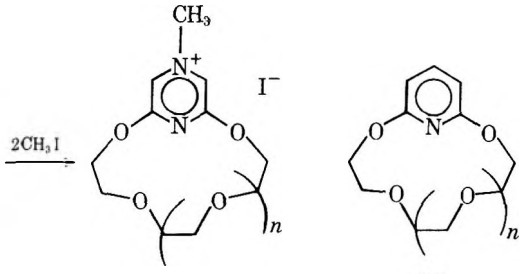
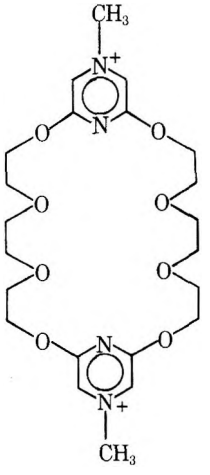


34, n = 1
35, n = 2
36, n = 3

38

pyridine macrocycles **38** (n = 1–4) also did not undergo quaternization under similar reaction conditions.[16]

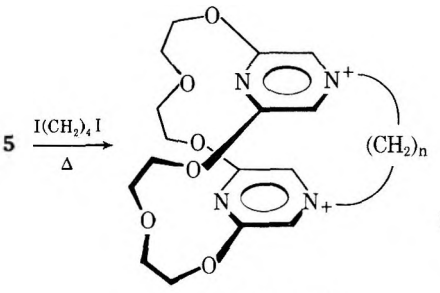
Similarly, when 2:2 macrocycle **11** was heated with excess methyl iodide, the dimethiodide **39** was isolated, in which only



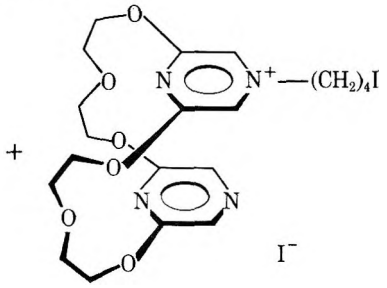
39

the two N-4 positions were alkylated. The NMR spectrum of **39** when compared to **11** indicated the expected downfield shift of the H-3,5 proton absorption (δ 8.37).

Since both N-4 positions undergo facile quaternization, the 2:2 macrocycle **5** was treated with 1,4-iodobutane for 5 h at 100 °C, resulting in the formation of a novel new series of cyclophanes, e.g., **40**. The 1:1 cyclophane **40** was isolated from a complex mixture of predominately the 1:1 monoquaternized compound **41** along with numerous polyquaternary products. The structure of **40** is substantiated by its symmetrical NMR spectrum which shows a downfield singlet at δ 8.14 for the pyrazine ring protons, whereas **41** possesses two (1:1) singlets



40, $n = 4$



41

at δ 8.12 and 7.65 for the quaternized and free pyrazine ring protons, respectively. The chemistry of this class of 1,3,5-bridged cyclophanes will be the topic of a forthcoming publication.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared (IR) and ultraviolet (UV) spectra were recorded on Beckman IR-7 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, ^{1}H NMR spectra were in deuteriochloroform solutions with Me_4Si as internal standard (δ = 0 ppm) whereas quaternary salts were in D_2O with an external standard and recorded on either Varian A-60A or HA-100 spectrometers. Molecular weights were determined with a Hewlett-Packard 302 vapor pressure osmometer and/or a Hitachi-Perkin-Elmer RMS-4 mass spectrometer. The recorded R_f values were determined by a standardized thin-layer chromatograph (TLC) procedure: 0.25-mm Brinkman silica gel HF eluting with cyclohexane–ethyl acetate (1:1). For preparative TLC, 2-mm Brinkman silica gel PF-254-366 plates were used, eluting with the stipulated solvent system. Elemental analyses were performed by Mr. R. Seab in these laboratories.

All reaction solvents were distilled from lithium aluminum hydride or sodium under nitrogen. Sodium hydride (57% oil dispersion) was initially washed with petroleum ether (bp 30–60 °C) and then dried in vacuo prior to the reaction.

Ethylene glycol and di-, tri-, and tetraethylene glycols were purchased from Aldrich Chemical and were distilled in vacuo prior to use. 3,6,9,12-Tetraoxa-1,14-tetradecanediol [pentaethylene glycol, bp 185–190 °C (0.15 mm) (lit.[13] bp 174–176 °C (0.14 mm)] and 3,6,9,12,15-pentaoxa-1,17-octadecanediol [hexaethylene glycol, bp 201–205 °C (0.7 mm) (lit.[13] bp 203.0–205.0 °C (0.3 mm)] were prepared according to the procedure of Perry and Hibbert.[13a]

Ethanedithiol, bis(2-mercaptoethyl) ether, and bis(2-mercaptoethyl) sulfide were purchased from Fairfield Chemical Co. and were used directly without further purification.

Although the noncyclized products could in most cases be isolated, in general complete characterization was undertaken only when they were a major product of the reaction. The cited yield data are based on analytically pure components and are not maximized.

Reaction of 2,6-Dichloropyrazine with Diethylene Glycol. General Procedure. To a suspension of oil-free sodium hydride (480 mg, 20 mmol) in anhydrous xylene (200 mL), diethylene glycol (1.10 g, 10 mmol) was added slowly with stirring under nitrogen. After 15

min, a solution of 2,6-dichloropyrazine (1.5 g, 10 mmol) in xylene (50 mL) was added, then the mixture was refluxed for 24 h. The reaction was cooled and the unreacted sodium hydride, if any, was carefully decomposed with water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford a viscous residue which was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (1:1), to give the following components.

Fraction A gave unreacted 2,6-dichloropyrazine, mp 51–52 °C.

Fraction B afforded 2:2 macrocycle **5**, which was recrystallized from 95% ethanol as colorless plates: mp 137–138 °C; 75 mg (4%); R_f 0.2; NMR ($CDCl_3$) δ 3.85 (t, β-CH_2O, J = 5 Hz, 8 H), 4.5 (t, α-CH_2O, J = 5 Hz, 8 H), 7.75 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2950, 1560, 1440, 1350, 1300, 1220, 1060, 850 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.49; N, 15.38; mol wt 364. Found: C, 52.47; H, 5.56; N, 15.26; mol wt (MS) m/e 364 (M^+).

Fraction C yielded 3:3 macrocycle **6**, which was recrystallized from 95% ethanol as colorless needles: mp 111–112 °C; 90 mg (5%); R_f 0.07; NMR ($CDCl_3$) δ 3.80 (t, β-CH_2O, J = 5 Hz, 12 H), 4.42 (t, α-CH_2O, J = 5 Hz, 12 H), 7.8 (s, 3,5-pyrazine-H, 6 H); IR ($CHCl_3$) 2900, 1590, 1540, 1300, 1280, 1180, 1050, 850 cm^{-1}.

Anal. Calcd for $C_{24}H_{30}N_6O_9$: C, 52.74; H, 5.49; N, 15.38; mol wt 546. Found: C, 52.42; H, 5.49; N, 15.42; mol wt (MS) m/e 546 (M^+).

The combined baselines from the preparative plates were extracted with ethanol–chloroform (1:1). The residue was rechromatographed (TLC), eluting three times with cyclohexane–ethyl acetate (1:2) to afford the 4:4 macrocycle **7**, as a beige solid, which was recrystallized from 95% ethanol to give colorless needles: mp 115–116 °C; 55 mg (3%); R_f 0.03; NMR ($CDCl_3$) δ 3.87 (t, β-CH_2O, J = 5 Hz, 16 H), 4.4 (t, α-CH_2O, J = 5 Hz, 16 H), 7.75 (s, 3,5-pyrazine-H); IR ($CHCl_3$) 2910, 1520, 1410, 1340, 1250, 1180, 1050, 850 cm^{-1}.

Anal. Calcd for $C_{32}H_{40}N_8O_{12}$: C, 52.74; H, 5.49; N, 15.38; mol wt 728. Found: C, 52.70; H, 5.59; N, 15.07; mol. wt. (MS) m/e 728 (M^+).

Diquaternization of 5 with 1,4-Diiodobutane. A mixture of macrocycle **5** (370 mg, 1 mmol) and 1,4-diiodobutane (310 mg, 1 mmol) in ethanol (25 mL) was refluxed for 24 h. After cooling, a yellow solid, which separated, was filtered and washed several times with anhydrous ether and finally recrystallized from ethanol to afford cyclophane **40**, as yellow needles: mp 214 °C (dec), 500 mg (80%); NMR (D_2O) δ 3.95 (m, β-CH_2O; β-CH_2, 12 H), 4.60 (m, α-CH_2O, 8 H), 5.25 (m, α-CH_2, 4 H), 8.14 (s, 3,5-pyrazine-H, 4 H).

Anal. Calcd for $C_{20}H_{28}N_4O_6I_2$: C, 35.60; H, 4.15; N, 8.30. Found: C, 35.50; H, 4.20; N, 8.25.

The mother liquor after concentration gave a pale yellow crystalline mass corresponding to **41**: mp 198 °C (dec); 60 mg (5%); NMR (D_2O) δ 2.4 (m, β,γ-CH_2, 4 H), 3.9 (br t, β-CH_2O, δ-CH_2, 10 H), 4.62 (br t, α-CH_2O, 8 H), 5.2 (br t, α-CH_2N^+, 2 H), 7.65 (s, free pyrazine-ring H, 2 H), 8.12 (s, charged pyrazine-ring H, 2 H). Attempted recrystallization failed to afford an analytical sample.

Reaction of 2,6-Dichloropyrazine with Triethylene Glycol. The above general procedure was followed except for the substitution of triethylene glycol (10 mmol). The crude reaction mixture was chromatographed (TLC) eluting three times with cyclohexane–ethyl acetate (1:1) to afford the following fractions.

Fraction A afforded a small quantity (10 mg) of unreacted dichloropyrazine, mp 51–52 °C.

Fraction B afforded 6,6′-dichloro-2,2′-[oxytris(ethylenoxy)]dipyrazine (**12**) as colorless flakes (recrystallized from absolute ethanol): mp 58–60 °C; 100 mg (2%); R_f 0.4; NMR δ 3.7 (s, γ-CH_2O, 4 H), 3.85 (t, β-CH_2O, J = 5 Hz, 4 H), 4.55 (t, α-CH_2O, J = 5 Hz, 4 H), 8.05 (s, 3-pyrazine-H, 2 H), 8.10 (s, 5-pyrazine-H, 2 H); IR ($CHCl_3$) 2900, 1570, 1540, 1430, 1410, 1360, 1300, 1175, 1125, 1100, 1050, 1000, 990, 880, 750 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_4O_4Cl_2$: C, 44.80; H, 4.26; N, 14.93; mol wt 375. Found: C, 44.71; H, 4.26; N, 14.74; mol wt (MS) m/e 375 (M^+).

Fraction C gave 1:1 macrocycle **10** as a white solid, which was recrystallized from 95% ethanol as colorless needles: mp 128–130 °C; 80 mg (2.5%); R_f 0.18; NMR ($CDCl_3$) δ 3.65 (s, γ-CH_2O, 4 H), 3.8 (t, β-CH_2O, J = 5 Hz, 4 H), 4.6 (t, α-CH_2O, J = 5 Hz, 4 H), 7.7 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2930, 1580, 1540, 1480, 1340, 1210, 1180, 1050, 920, 830 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.38; mol wt 226. Found: C, 53.01; H, 6.23; N, 12.24; mol wt (osmometry) 229.5 (average).

The methiodide of **10** was prepared: a mixture of **10** (113 mg) was heated with methyl iodide (0.5 mL) in a sealed tube for 8 h at 90 °C. Excess of methyl iodide was evaported and the residue was crystallized from ethanol as pale yellow needles: mp 203 °C (dec); 150 mg (90%); NMR (D_2O) δ 3.85 (s, γ-CH_2O, 4 H), 3.95 (m, β-CH_2O–, 4 H), 4.3 (s, N-Me, 3 H), 4.95 (t, α-CH_2O, J = 5 Hz, 4 H), 8.15 (s, 3,5-pyrazine-H, 2 H).

Anal. Calcd for $C_{11}H_{17}N_2O_4I$: C, 35.86; H, 4.61; N, 7.60. Found: C, 35.70; H, 4.72; N, 7.47.

Fraction D yielded 2:2 macrocycle **11**, which was recrystallized from 95% ethanol as colorless needles: mp 138–140 °C; 200 mg (8%); R_f 0.12; NMR ($CDCl_3$) δ 3.70 (s, γ-CH_2O, 8 H), 3.85 (t, β-CH_2O, J = 5 Hz, 8 H), 4.5 (t, α-CH_2O, J = 5 Hz, 8 H), 7.8 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1580, 1500, 1450, 1400, 1300, 1280, 1160, 1110, 950, 850 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}N_4O_8$: C, 53.09; H, 6.19; N, 12.38; mol wt 452. Found: C, 53.02; H, 6.53; N, 12.20; mol wt (osmometry) 436 (av).

The dimethiodide **39** was prepared: a mixture of **11** (113 mg) and methyl iodide (0.5 mL) was heated in a sealed tube for 8 h. The crystalline residue was recrystallized from ethanol as yellow needles: mp 211 °C (dec); 132 mg (75%); NMR (D_2O) δ 3.75 (s, γ-CH_2O, 8 H), 3.9 (m, β-CH_2O, 8 H), 4.45 (s, N-CH_3, 6 H), 4.75 (t, α-CH_2O, J = 5 Hz, 8 H), 8.37 (s, 3,5-pyrazine-H, 4H); IR ($CHCl_3$) 2950, 1540, 1490, 1450, 1370, 1320, 1240, 1210, 1150, 1050, 940, 830 cm^{-1}.

Anal. Calcd for $C_{22}H_{34}N_4O_8I_2$: C, 35.86; H, 4.61; N, 7.60. Found: C, 35.72; H, 4.48; N, 7.52.

Reaction of 2,6-Dichloropyrazine with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol (1.94 g, 10 mmol). The crude reaction mixture was chromatographed (TLC), eluting four times with cyclohexane–ethyl acetate (1:1), to give the following fractions.

Fraction A afforded unreacted 2,6-dichloropyrazine, mp 51–52 °C.

Fraction B gave 1:1 macrocycle **13**, which was recrystallized from ethanol as colorless plates: mp 86–87 °C; 100 mg (3%); R_f 0.12; NMR ($CDCl_3$) δ 3.54 (m, γ-CH_2O, 8 H), 3.85 (t, β-CH_2O, J = 5 Hz, 4 H), 4.61 (t, α-CH_2O, J = 5 Hz, 4 H), 7.75 (so 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2910, 1545, 1350, 1280, 1145, 1050, 940, 850 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.66; N, 10.37; mol wt 270. Found: C, 53.30; H, 6.81; N, 10.10; mol wt (osmometry) 272.8 (av).

The monomethiodide of **13** was prepared: macrocycle **13** (270 mg, 10 mmol) was heated with excess methyl iodide in a sealed tube at 80 °C for 8 h. Excess methyl iodide was evaporated, and the yellow residue was washed several times with anhydrous ether to remove unreacted starting materials and then recrystallized from ethanol to afford **35** as yellow needles: mp 186–189 °C (dec); 400 mg (95%); NMR ($CDCl_3$) δ 3.58 (s, γ-CH_2O, 8 H), 3.85 (m, β-CH_2O, 4 H), 4.6 (s, N-Me, 3 H), 4.75 (m, α-CH_2O, 4 H), 8.35 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2950, 1525, 1500, 1450, 1325, 1230, 1110, 1052, 950, 850 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}N_2O_5I$: C, 37.86; H, 5.09; N, 6.79. Found: C, 37.70; H, 5.13; N, 6.69.

Fraction C was initially isolated as an oil; however, upon dissolution in alcohol and prolonged standing (ca. 1 week) 2:2 macrocycle **14** crystallized: mp 75–76 °C; 75 mg (3%); R_f 0.05; NMR ($CDCl_3$) δ 3.62 (m, γ-CH_2O, 16 H), 3.8 (t, β-CH_2O, J = 5 Hz, 8 H), 4.4 (t, α-CH_2O, J = 5 Hz, 8 H), 7.75 (s, 3,5-pyrazine-H, 4 H).

Anal. Calcd for $C_{24}H_{36}N_4O_{10}$: C, 53.33; H, 6.66; N, 10.37; mol wt 540. Found: C, 53.23; H, 6.63; N, 10.16; mol wt (osmometry) 540 (av).

Reaction of 2,6-Dichloropyrazine with Pentaethylene Glycol. The general procedure was followed except for the substitution of pentaethylene glycol (2.38 g, 10 mmol). After standard workup procedures, the reaction residue was chromatographed (TLC), eluting four times with cyclohexane–ethyl acetate (1:1), to afford the following fractions.

Fraction A gave unreacted 2,6-dichloropyrazine, mp 51–52 °C.

Fraction B was recrystallized from ethanol to afford 1:1 macrocycle **15** as colorless plates: mp 86–87 °C; 50 mg (1%).

Fraction C afforded after recrystallization from 95% ethanol the desired 1:1 macrocycle **17**: mp 72–74 °C; 100 mg (4%); R_f 0.11; NMR ($CDCl_3$) δ 3.55 (br d, γ,ϵ-CH_2O, 12 H), 3.85 (t, β-CH_2O, J = 5 Hz, 4 H), 4.5 (t, α-CH_2O–, J = 5 Hz, 4 H), 7.72 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2950, 1600, 1540, 1450, 1430, 1300, 1250, 1175, 1050, 940, 840 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.50; H, 7.00; N, 8.91; mol wt 314. Found: C, 53.21; H, 6.98; N, 8.63; mol wt (MS) m/e 314 (M^+).

The monomethiodide **36** was prepared from the macrocycle **17** (160 mg) with methyl iodide (0.5 mL) by heating in a sealed tube on a water bath for 5 h. After removing unquaternized macrocycle by repeated washing with anhydrous ether, a residue was recrystallized from ethanol, affording **36** as yellow needles: mp 204 °C (dec); 180 mg (70%); NMR (D_2O) 3.6 (br d, γ,ϵ-CH_2O, 12 H), 3.95 (t, β-CH_2O–, J = 5 Hz, 4 H), 4.65 (t, α-CH_2O–, J = 5 Hz, 4 H), 8.35 (s, 3,5-Pyr-H, 2 H).

Anal. Calcd for $C_{15}H_{25}N_2O_6I$: C, 39.47; H, 5.48; N, 6.14. Found: C, 39.21; H, 5.56; N, 6.10.

The baseline was extracted with a solvent mixture of chloroform

and ethanol (1:1) and the residue rechromatographed (TLC), eluting four times with cyclohexane–ethyl acetate (1:2), to afford 2:2 macrocycle **18** as colorless crystalline plates: mp 80–81 °C; 60 mg (2%); R_f 0.04; NMR ($CDCl_3$) δ 3.60 (br d, γ,ϵ-CH_2O, 24 H), 3.85 (t, β-CH_2O, J = 5 Hz, 8 H), 4.5 (t, α-CH_2O–, J = 5 Hz, 8 H), 7.80 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1600, 1570, 1440, 1300, 1230, 1100, 1070, 1050, 950, 840 cm^{-1}.

Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 53.50; H, 7.00; N, 8.91; mol wt 628. Found: C, 53.36; H, 8.72; mol wt (osmometry) 600 (av).

Reaction of 2,6-Dichloropyrazine with Hexaethylene Glycol. The general procedure was followed except for the substitution of hexaethylene glycol (2.82 g, 10 mmol). The reaction residue, after standard workup, was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (1:1). The following fractions were isolated and characterized.

Fraction A gave unreacted 2,6-dichloropyrazine, mp 52 °C.

Fraction B afforded 30 mg of a crystalline compound, which corresponded physically and spectrally to 1:1 macrocycle **10**, mp 130–131 °C.

Fraction C afforded 1:1 macrocycle **13**, which was recrystallized from 95% ethanol as colorless plates: mp 86–87 °C; 30 mg (<1%).

The residual baseline was extracted with chloroform–ethanol (1:1), and then after concentration the residue was rechromatographed (TLC), eluting three times with cyclohexane–ethyl acetate (1:3) to give the following fractions.

Fraction D was recrystallized from petroleum ether (bp 60–90 °C), affording colorless needles of 1:1 macrocycle **19**: mp 59–60 °C; 500 mg (15%); R_f 0.08; NMR ($CDCl_3$) δ 3.65 (m, γ,ω-CH_2O, 16 H), 3.82 (t, β-CH_2O, J = 5 Hz, 4 H), 4.52 (t, α-CH_2O, J = 5 Hz, 4 H), 8.71 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2900, 1590, 1530, 1440, 1380, 1270, 1180, 1025, 950, 850 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}N_2O_7$: C, 53.63; H, 7.26; mol wt 358. Found: C, 53.45; H, 7.42; mol wt (MS) m/e 358 (M^+).

Fraction E was obtained as colorless plates (recrystallized from ethanol) corresponding to 2:2 macrocycle **20**: mp 68–69 °C; 80 mg (2%); R_f 0.03; NMR ($CDCl_3$) δ 3.6 (m,γ,ω-CH_2O, 32 H), 3.8 (t, β-CH_2O–, J = 5 Hz, 8 H), 4.5 (t, α-CH_2O–, J = 5 Hz, 8 H), 8.75 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1590, 1540, 1425, 1320, 1250, 1200, 1145, 1100, 1050, 1000, 930, 850, 750 cm^{-1}.

Anal. Calcd for $C_{32}H_{52}N_4O_{14}$: C, 53.63; H, 7.26; N, 7.92; mol wt 716. Found: C, 53.39; H, 7.35; N, 7.63; mol wt (osmometry) 678 (av).

Reaction of 2,6-Dichloropyrazine with Ethylene Glycol. Method A. With Sodium Hydride. To a stirred suspension of oil-free sodium hydride (2 g, 80 mmol) in anhydrous xylene (300 mL), ethylene glycol (2.5 g, 40 mmol) was added dropwise under argon. The mixture was stirred for 30 min, and then a xylene solution of 2,6-dichloropyrazine (6 g, 40 mmol) was added over 10 min. The mixture was refluxed for 24 h and worked up as previously described. The gummy residue was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (1:1), affording the following fractions.

Fraction A gave unreacted 2,6-dichloropyrazine, mp 52 °C.

Fraction B was recrystallized from 95% ethanol as colorless needles of 6,6′-dichloro-2,2′-(ethylenedioxy)dipyrazine (**21**): mp 125–126 °C; 150 mg (3%); R_f 0.5; NMR ($CDCl_3$) δ 4.75 (s, –OCH_2CH_2O–, 4 H), 8.15 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1550, 1425, 1400, 1300, 1175, 1075, 925 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_4O_2Cl_2$: C, 41.11; H, 2.78; N, 19.51; mol wt 287. Found: C, 41.15; H, 2.72; N, 19.49; mol wt (MS) 287 (M^+).

Fraction C afforded 2,6-bis(6′-chloro-2′-pyrazyloxyethylenoxy)-pyrazine (**22**) as colorless needles (95% ethanol): mp 115–116 °C; 100 mg (2%); R_f 0.35; NMR ($CDCl_3$) δ 4.7 (s, –OCH_2CH_2O–, 8 H), 7.82 (s, 3,5-pyrazine-H, 2 H), 8.2 (s, 3′,5′-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1550, 1500, 1400, 1300, 1250, 1175, 1000, 950, 850 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}N_6O_4Cl_2$: C, 45.17; H, 3.29; N, 19.76; mol wt 425. Found: C, 45.39; H, 3.18; N, 19.72; mol wt (MS) m/e 425 (M^+).

Fraction D was shown to be 2-(6′-chloro-2′-pyrazyloxy)ethanol (**9**), as a brown viscous oil: bp 103–104 °C (0.1 mm, short path); 250 mg (4%); R_f 0.2; NMR ($CDCl_3$) δ 3.5 [s, –OH (exchanged with D_2O), 1 H], 3.95 (m, β-CH_2O, 2 H), 4.45 (m, α-CH_2O, 2 H), 8.15 (s, 3′,5′-pyrazine-H, 2 H); IR (neat) 3150, 2975, 1525, 1475, 1300, 1275, 1145, 1050, 945, 840 cm^{-1}.

Anal. Calcd for $C_6H_7N_2O_2Cl$: C, 41.26; H, 4.01; N, 16.04; mol wt 174.5. Found: C, 41.03; H, 4.16; N, 15.87; mol wt (osmometry) 172 (av).

Fraction E afforded the tetrapyrazyl dichloride **23** as lemon-yellow plates, which were recrystallized from 95% ethanol: mp 143–145 °C; 60 mg (1%); R_f 0.17; NMR ($CDCl_3$) δ 4.6 (s, –OCH_2CH_2O–, 12 H), 7.85 (s, 3′,5′-pyrazine-H, 4 H), 8.2 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1550, 1500, 1450, 1300, 1250, 1155, 1045, 1000, 850 cm^{-1}.

Anal. Calcd for $C_{22}H_{20}N_8O_6Cl_2$: C, 46.89; H, 3.55; N, 19.89; mol wt 563. Found: C, 46.75; H, 3.58; N, 19.61; mol wt (MS) m/e 563 (M^+).

Fraction F was isolated as a viscous oil shown to be **24**: bp 125–126 °C (0.8 mm, short path); 125 mg (2%); R_f 0.10; NMR ($CDCl_3$) δ 3.7 [s, –OH (exchanged with D_2O), 1 H], 3.90 (t, β-CH_2O, J = 4 Hz, 2 H), 4.45 (t, α-CH_2O, J = 4 Hz, 2 H), 4.75 (s, –OCH_2CH_2O–, 4 H), 7.85 (s, 3,5-pyrazine-H, 2 H), 8.2 (s, 3′,5′-pyrazine, 2 H); IR (neat) 3400, 2900, 1575, 1525, 1400, 1300, 1000, 850 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}N_4O_4Cl$: C, 46.09; H, 4.19; mol wt 312.5. Found: C, 45.96; H, 4.17; mol wt (osmometry) 320 (av).

Fraction G was recrystallized from 95% ethanol as a microcrystalline solid and shown to be **25**: mp 125–127 °C; 200 mg (3%); R_f 0.07; NMR ($CDCl_3$) δ 3.75 [s, –OH (exchanged with D_2O), 1 H], 3.95 (m, β-CH_2O, 2 H), 4.4 (m, α-CH_2O, 2 H), 4.55 (s, –OCH_2CH_2O–, 8 H), 7.8 (s, 3,3′,5,5′-pyrazine-H, 4 H), 8.15 (s, 3″,5″-pyrazine-H, 2 H); IR ($CHCl_3$) 3300, 2900, 1525, 1475, 1375, 1250, 1150, 1000, 740 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_6O_6Cl$: C, 47.90; H, 4.25; N, 18.64; mol wt 450.5. Found: C, 47.84; H, 4.17; N, 18.49; mol wt (osmometry) 444 (av).

Method B. With Lithium Hydride. To a suspension of lithium hydride (0.64 g, 80 mmol) in anhydrous xylene (400 mL), ethylene glycol (2.5 g, 40 mmol) was added dropwise. To this warm suspension, 2,6-dichloropyrazine (6 g, 40 mmol) was added and the mixture was refluxed for 24 h. The workup procedure mimicked the general procedure, and the crude reaction products were chromatographed (TLC) affording the same noncyclic products, except product distribution: **21** (mp 125–126 °C; 5%), **22** (mp 115–116 °C; 1%), **23** (mp 143–145 °C; 2%), **9** [bp 103–104 °C (0.1 mm, short path); 5%], and **25** (mp 125–127 °C; 1%). Compound **24** was not isolated in this reaction.

Reaction of 2,6-Dichloropyrazine with Bis(2-mercaptoethyl) Ether. The above general procedure was followed except for the substitution of bis(2-mercaptoethyl) ether (10 mmol) with 2,6-dichloropyrazine (10 mmol). After the workup, the residue was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (4:1), to afford two macrocycles along with starting material.

Fraction A gave a small amount (<20 mg) of unreacted 2,6-dichloropyrazine: mp 52 °C.

Fraction B afforded 1:1 macrocycle **26a** as colorless plates (recrystallized from ethanol): mp 118–119 °C; 100 mg (4%); R_f 0.6; NMR ($CHCl_3$) δ 3.25 (t, β-CH_2O. J = 4 Hz, 4 H), 3.91 (t, α-CH_2O, J = 4 Hz, 4 H), 8.17 (s, 3,5-pyrazine-H, 2 H); IR ($CHCl_3$) 2850, 1480, 1390, 1180, 1140, 1100, 990, 840 cm^{-1}.

Anal. Calcd for $C_8H_{10}N_2S_2O$: C, 44.85; H, 4.67; N, 13.08; mol wt 214. Found: C, 44.56; H, 4.72; N, 12.86; mol wt (MS) m/e 214 (M^+).

Fraction C was recrystallized from 95% ethanol to afford 2:2 macrocycle **27** as colorless needles: mp 155–156 °C; 140 mg (6%); R_f 0.5; NMR ($CDCl_3$) $\delta \sim$ 3.5 (m, α- and β-CH_2O, 16 H); 8.1 (s, 3,5-pyrazine-H, 4 H); IR ($CHCl_3$) 2900, 1500, 1450, 1250, 1140, 1080, 990, 830 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_4S_4O_2$: C, 44.85; H, 4.67; N, 13.08; mol wt 428. Found: C, 44.80; H, 4.92; N, 12.83; mol wt (osmometry) 430 (av).

Reaction of 2,6-Dichloropyrazine with Bis(2-mercaptoethyl) Sulfide. The general procedure was followed except for the substitution of bis(2-mercaptoethyl)sulfide (1.54 g, 10 mmol). The crude reaction mixture was chromatographed (TLC), eluting two times with cyclohexane–ethyl acetate (20:1) to afford the major fast-moving 2[2-[2-(6-chloropyrazylthio)]thioethoxy]ethanethiol (**28**) as a colorless viscous oil: bp 145 °C (0.5 mm; short path); 210 mg (8%); R_f 0.85; NMR ($CDCl_3$) δ 1.77 [m, –SH (exchanged slowly with D_2O), 1 H], 2.8 (m, $SCH_2CH_2SCH_2$, 6 H), 3.35 (m, S-α-CH_2, 2 H), 8.18 (s, 3-pyrazine-H, 1 H), 8.30 (s, 5-pyrazine-H, 1 H), IR (neat) 2900, 2550, 1540, 1490, 1400, 1350, 1260, 1190, 1150, 1100, 990, 860, 830, 740 cm^{-1}.

Anal. Calcd for $C_8H_{11}N_2S_3Cl$: C, 36.02; H, 4.12; N, 10.60; mol wt 266.5. Found: C, 35.93; H, 4.06; N, 10.38; mol wt (osmometry) 272 (av).

The baseline was extracted with a mixture of chloroform–ethanol (1:1) and after concentration the residue was rechromatographed (TLC), eluting three times with cyclohexane–ethyl acetate (10:1) to afford the following fractions.

Fraction B afforded **29** as a viscous oil: bp 162 °C (0.5-mm short path); 80 mg (2%); R_f 0.70; NMR ($CDCl_3$) δ 1.71 [m, –SH (exchanged slowly with D_2O), 1 H], 2.9 [m, –$CH_2S(CH_2)_2S(CH_2)_2$–, 10 H], 3.35 (m, α-SCH_2, 2 H), 8.25 (s, 3-pyrazine-H, 1 H), 8.35 (s, 5-pyrazine-H, 1 H), IR (neat) 2900, 2550, 1490, 140, 1400, 1375, 1350, 1260, 1190, 1120, 1040, 990, 850, 830, 750 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}N_2S_4Cl$: C, 36.75; H, 4.58; N, 8.57; mol wt 326.5. Found: C, 37.00; H, 4.49; N, 8.68; mol wt (osmometry) 338 (av).

Fraction C afforded **30** as a viscous oil: bp 187 °C (1-mm short path); 55 mg (2%); R_f 0.65; NMR ($CDCl_3$) 2.9 (m, CH_2SCH_2, 8 H), 3.4

(m, α-SCH_2, 4 H), 8.19 (s, 3-pyrazine-H, 2 H), 8.36 (s, 5-pyrazine-H, 2 H); IR (neat) 2910, 1700, 1500, 1475, 1390, 1350, 1250, 1175, 1125, 990, 860, 830, 750 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_4S_4Cl_2$: C, 38.10; H, 3.64; N, 12.75; mol wt 439. Found: C, 38.35; H, 3.71; N, 12.45; mol wt (osmometry) 446 (av).

Reaction of 2,6-Dichloropyrazine with Ethanedithiol. The general procedure was followed except for the substitution of ethanedithiol (940 mg, 10 mmol). The gummy residue, after usual workup, was chromatographed (TLC), eluting with cyclohexane–ethyl acetate (4:1) to afford the following fractions.

Fraction A gave 2-(6′-chloro-2′-pyrazylthio)ethanethiol (**32**) as pale yellow microcrystals (recrystallized from 95% ethanol): mp 91 °C; 70 mg (4%); R_f 0.52; NMR ($CDCl_3$) δ 1.7 [t, –SH (exchanged slowly with D_2O), 1 H], 2.9 (t, β-CH_2O–, J = 5 Hz, 2 H), 3.4 (t, α-CH_2O–, J = 5 Hz, 2 H), 8.15 (s, 3-pyrazine-H, 1 H), 8.35 (s, 5-pyrazine-H, 1 H); IR ($CHCl_3$) 2900, 1480, 1390, 1350, 1340, 1250, 1175, 1150, 1125, 1080, 990, 860, 830, 720 cm^{-1}.

Anal. Calcd for $C_6H_7N_2S_2Cl$: C, 34.86; H, 3.38; N, 14.04; mol wt 206.5. Found: C, 34.75; H, 3.21; N, 13.80; mol wt (osmometry) 208 (av).

Fraction B was recrystallized from ethanol as pale yellow needles of 6,6′-dichloro-2,2′-(ethylenedithio)dipyrazine (**33**): mp 106 °C; 100 mg (6%); R_f 0.43; NMR ($CDCl_3$) δ 4.55 (s, SCH_2CH_2S, 4 H), 8.4 (s, 3,3′-pyrazine-H, 2 H), 8.5 (s, 5,5′-pyrazine-H, 2 H); IR ($CHCl_3$) 2980, 1540, 1500, 1375, 1175, 1150, 1125, 990, 960, 830, 740 cm^{-1}.

Anal. Calcd for $C_{10}H_8H_{N4}S_2Cl_2$: C, 37.61; H, 2.50; N, 17.55; mol wt 319. Found: C, 37.42; H, 2.46; N, 17.46; mol wt (osmometry) 322 (av).

Acknowledgments. The authors gratefully acknowledge partial support of the preliminary aspects of this work by the Public Health Service grant from the National Institutes of Health and Merck Sharp and Dohme Co.

Registry No.—**5**, 64332-24-7; **6**, 64332-22-5; **7**, 64332-23-6; **9**, 64332-21-4; **10**, 64332-20-3; **11**, 64332-19-0; **12**, 64332-18-9; **13**, 64332-32-7; **14**, 64332-31-6; **17**, 64332-30-5; **18**, 64332-29-2; **19**, 64332-28-1; **20**, 64332-27-0; **21**, 64332-26-9; **22**, 64332-25-8; **23**, 64332-17-8; **24**, 64332-16-7; **25**, 64332-15-6; **26a**, 64332-14-5; **27**, 64332-13-4; **28**, 64332-12-3; **29**, 64332-11-2; **30**, 64332-10-1; **32**, 64332-09-8; **33**, 64332-08-7; **34**, 64332-07-6; **35**, 64332-06-5; **39**, 64332-05-4; **40**, 64332-04-3; **41**, 64332-03-2; diethylene glycol, 111-46-6; 2,6-dichloxapyrazine, 4774-14-5; triethylene glycol, 112-27-6; methyl iodide, 74-88-4; tetraethylene glycol, 112-60-7; hexaethylene glycol, 2615-15-8; bis(2-mercaptoethyl) ether, 2150-02-9; bis(2-mercaptoethyl) sulfide, 3570-55-6; ethanedithiol, 540-63-6.

References and Notes

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Organic Metals. A Study of the Hurtley–Smiles Tetrathiafulvalene Synthesis

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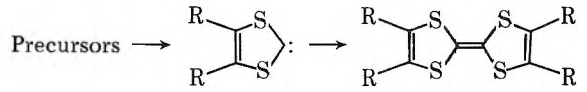
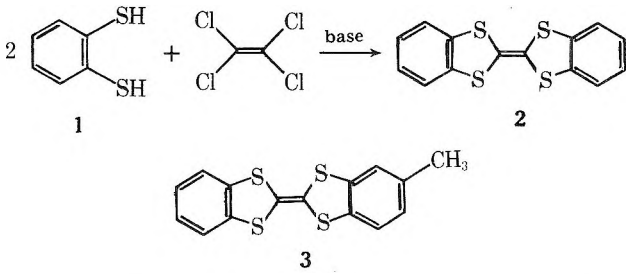
Received July 25, 1977

The reaction of excess tetrachloroethylene with *o*-benzenedithiol (**1**) and with disodium *cis*-ethenedithiolate (**6**) affords 2-dichloromethylene-4,5-benzo-1,3-dithiole (**4**) and 2-dichloromethylene-1,3-dithiole (**10**), respectively. Reaction of **1** with either **4** or **10** under basic conditions yields only dibenzotetrathiafulvalene (**2**). A similar reaction of **1** with tetrakis(carbomethoxy)tetrathiafulvalene (**12**) results in transdithiolation with the formation of **2** and 4,5-bis(carbomethoxy)-4′,5′-benzotetrathiafulvalene (**13**). Mechanisms of these reactions are discussed.

Since the first report on the high electrical conductivity of the charge-transfer salt of tetrathiafulvalene–tetracyanoquinodimethane (TTF–TCNQ) in 1973,[1] much interest has been generated in the synthesis of tetrathiafulvalene derivatives and analogues.[2] Almost all known tetrathiafulvalenes are symmetrical compounds, which are generally prepared by reactions involving the coupling of intermediary carbene or carbenoid monomers.[2]



In 1926, Hurtley and Smiles found that *o*-benzenedithiol (**1**) reacts with tetrachloroethylene under basic conditions to give dibenzotetrathiafulvalene (**2**).[3] This reaction, which represents the first synthesis of any tetrathiafulvalene, received no further attention until a half century later. At that time, improved reaction conditions were reported, and the reaction of tetrachloroethylene with a mixture of o-benzenedithiol and toluene-3,4-dithiol was found to give a mixture of products from which the pure mixed TTF derivative **3** could be crystallized.[4]



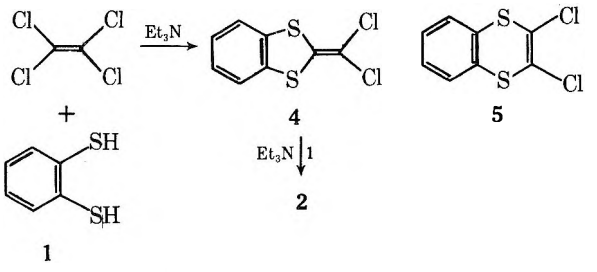
1 2

3

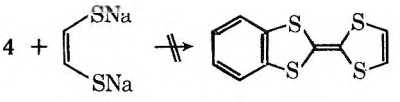
As part of a broad investigation of synthetic routes to unsymmetrical tetrathiafulvalenes,[5] we now report the results of a further study of the Hurtley–Smiles synthesis, aimed at its modification for the synthesis of monobenzotetrathiafulvalenes.[6]

Results

Dithiol **1**[7] was allowed to react with excess tetrachloroethylene and triethylamine in DMF at room temperature with the objective of isolating the intermediate dihalide in the Hurtley–Smiles reaction. Workup after 3 days afforded only a small amount of the symmetrical TTF **2** (5%), the major product (59%) being a colorless, crystalline compound, $C_8H_4S_2Cl_2$, mp 157–158 °C. This compound was assigned the structure 2-dichloromethylene-4,5-benzo-1,3-dithiole (**4**) rather than the isomeric benzodithiin structure **5**, since it was slowly converted in high yield to **2** on treatment with dithiol **1** and triethylamine in refluxing acetonitrile. On the other hand, attempts to convert **4** to monobenzotetrathiafulvalene (**7**) or its dinitrile **9** by reaction with disodium *cis*-ethenedithiolate (**6**)[8] or disodium *cis*-dicyanoethenedithiolate (**8**)[9] were unsuccessful, the starting dihalide being recovered unchanged.



1 4 5 2



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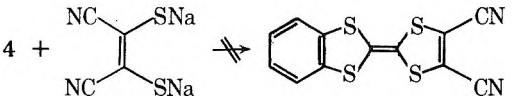
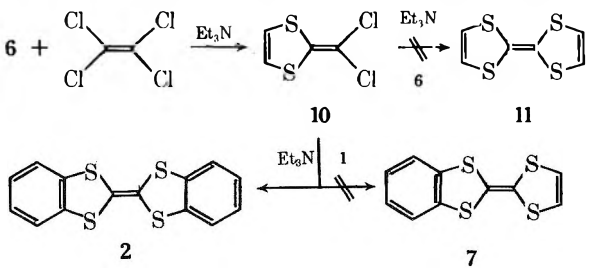


8 9

The dithiolate salt **6** was found to react with excess tetrachloroethylene in the presence of triethylamine to give a single isolable product (42%), mp 55–58 °C, assigned the structure 2-dichloromethylene-1,3-dithiole (**10**) by analogy with **4**. In contrast to **4**, which is quite stable to storage, dichloride **10** decomposes to a black tar on keeping overnight in the refrigerator; it rapidly turns blue on contact with silica, but it can be purified chromatographically on basic alumina. Attempts to convert **10** to tetrathiafulvalene (**11**) by further reaction with the salt **6** were unsuccessful, and led only to the destruction of **10**.

By contrast, dichloride **10** reacted with *o*-benzenedithiol (**1**) in the presence of triethylamine. The only isolable product (30%) was not, however, the expected monobenzotetrathiafulvalene (**7**),[6] but rather dibenzotetrathiafulvalene (**2**).



10 11 2 7

On the basis of mechanistic considerations of the above reaction (see Discussion), it seemed possible that each dichloromethylene unit of tetrachloroethylene might be re-

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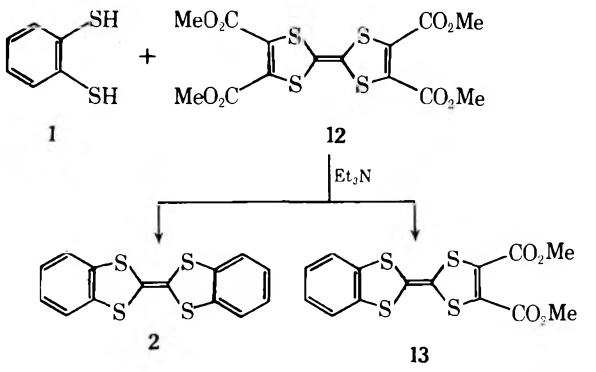
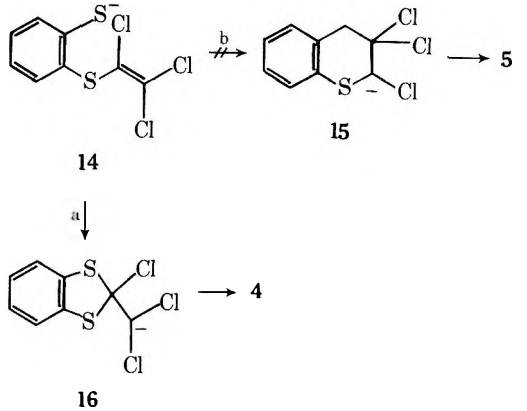
placeable by an electron-deficient 1,3-dithiole unit in the Hurtley–Smiles reaction. Indeed, reaction of excess *o*-benzenedithiol (**1**) with tetrakis(carbomethoxy)tetrathiafulvalene (**12**)[10] in the presence of triethylamine resulted in the quantitative conversion of tetraester **12** into dibenzotetrathiafulvalene (**2**). A similar reaction of equimolar quantities of **1** and **12** afforded a small amount (7%) of **2**, along with a modest



yield (19%) of 4,5-bis(carbomethoxy)-4′,5′-benzotetrathiafulvalene (**13**).[6] Since diester **13** is readily converted in one step to monobenzotetrathiafulvalene (**7**),[6] the latter is therefore accessible from readily prepared starting materials[7,10] by the use of this new "transdithiolation" synthesis.

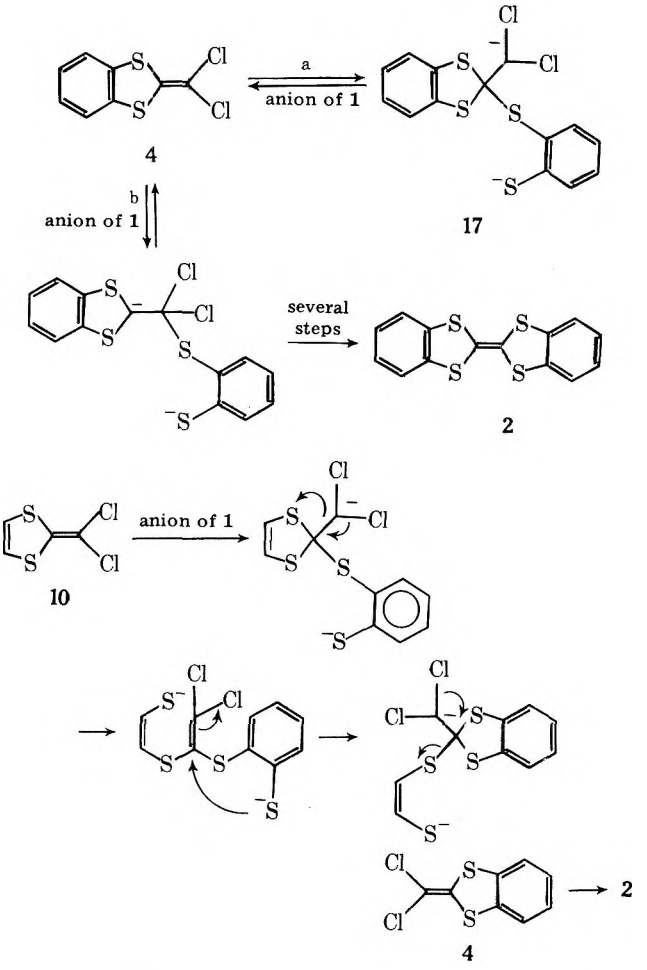
Discussion

The formation of the five-membered ring heterocycles **4** and **10** from tetrachloroethylene, rather than six-membered isomers (e.g., **5**), appears to fit formally within the framework of Baldwin's rules, although these rules are of doubtful predictive value when applied to anions of second-row elements.[11] The observed products are also explicable, however, on the basis of the greater electronegativity of chlorine as compared to sulfur. Thus, in the case of the reaction of o-benzenedithiol (**1**) with tetrachloroethylene, the structure of the final dichloride is determined by the point of attack (a or b) of the intermediary thiolate anion **14**. Path a should be of lower energy than path b due to the greater stability of carbanion **16** over the isomeric carbanion **15**.

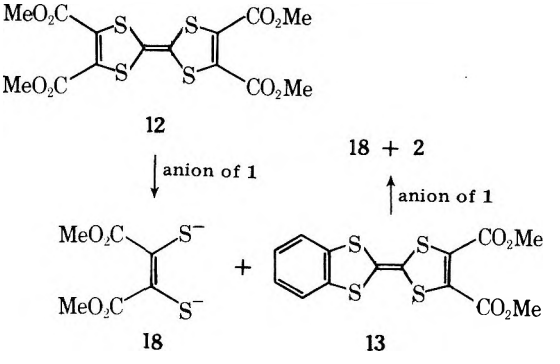


The electronegativity argument proposed above also explains why the anion of dithiol **1** reacts more slowly with dihalide **4** than it does with tetrachloroethylene. Thiolate attack on **4** should occur preferentially, *but reversibly*, by path a to give the more stable anion **17**; attack at the chlorine-bearing carbon (path b) should occur less often, but it will eventually lead to the formation of dibenzotetrathiafulvalene (**2**).

In accord with this mechanism, dichloride **10** will react preferentially with the anion of **1** at the sulfur-bearing carbon, resulting in transthiolation with the formation of dichloride **4**; further reaction of **4** with **1** then gives **2** as outlined above.



The reaction of the tetraester **12** with the anion of **1** may be viewed as an entirely analogous two-step transthiolation process. In this case, the leaving-group molecule is the anion **18** and the intermediate diester **13** was in fact detected when an insufficient quantity of dithiol **1** was employed.



Experimental Section

Melting points are uncorrected. NMR ($CDCl_3$ containing Me_4Si as internal standard), infrared (KBr), ultraviolet, and mass spectra were determined using Varian A-60, and Perkin-Elmer 137, 202 and 270B spectrometers, respectively.

2-Dichloromethylene-4,5-benzo-1,3-dithiole (4). *o*-Benzenedithiol[7] (3.6 g, 0.025 mol) and triethylamine (10.0 g, 0.10 mol) were dissolved in 100 mL of dimethylformamide, and tetrachloroethylene (16.8 g, 0.10 mol) was added dropwise with stirring at room temperature under an argon atmosphere. The reaction was allowed to proceed for 3 days at room temperature. The reaction mixture was poured into 300 mL of water and extracted with benzene. The benzene layer was washed with water, dried (Na_2SO_4), and evaporated to give a yellow oil. The oil was chromatographed on silica (hexane–benzene) to give 3.5 g of colorless needles of 2-dichloromethylene-4,5-benzo-1,3-dithiole (**4**, 59%) and 0.2 g of yellow crystals of dibenzotetrathiafulvalene (**2**, 5%). The water layer was acidified to pH 5 with hy-

drochloric acid and reextracted with benzene. The benzene layer was dried (Na_2SO_4) and concentrated to give 0.6 g of *o*-benzenedithiol (**1**, 17%).

2-Dichloromethylene-4,5-benzo-1,3-dithiole (**4**): mp 157–158 °C; UV (cyclohexane) λ_{max} 207 nm (ϵ 7700), 242 (15 000), 266 (9900), 277 (10 000), 314 (4200); NMR δ 7.16 (s); mass spectrum *m/e* (rel intensity) 238 (17), 236 (72), 234 (100), 199 (18), 164 (15).

Anal. Calcd for $C_8H_4S_2Cl_2$: C, 40.85; H, 1.70; S, 27.23; Cl, 30.21. Found: C, 40.84; H, 1.63; S, 27.00; Cl, 30.00.

The dibenzotetrathiafulvalene, mp 232–234 °C (lit.[3] 234 °C), was identical (IR) with an authentic sample.

Attempted Reaction of 2-Dichloromethylene-4,5-benzo-1,3-dithiole (4) with Disodium *cis*-Ethenedithiolate (6). 2-Dichloromethylene-4,5-benzo-1,3-dithiole (**4**, 60 mg, 0.25 mmol) and disodium *cis*-ethenedithiolate[8] (140 mg, 1 mmol) were dissolved in 10 mL of dimethylformamide, and the solution was stirred for 3 days at room temperature under an argon atmosphere. The reaction mixture was poured into 25 mL of water and extracted with benzene. The benzene layer was washed successively with dilute aqueous sodium hydroxide, water, dilute hydrochloric acid, and finally with water, dried ($MgSO_4$), and evaporated to give a brown solid. Chromatography on silica (hexane–benzene) afforded 55 mg of the starting material **4** as colorless needles, mp 157–158 °C.

2-Dichloromethylene-4,5-benzo-1,3-dithiole (60 mg) and disodium salt **6** (140 mg) were dissolved in 10 mL of acetonitrile, and the mixture was refluxed for 15 h under an argon atmosphere. The reaction mixture was worked up as above to give 57 mg of recovered starting material as colorless needles, mp 157–158 °C. Attempted reaction of **4** with salt **8**[9] led to similar results.

Reaction of 2-Dichloromethylene-4,5-benzo-1,3-dithiole (4) with o-Benzenedithiol (1). *o*-Benzenedithiol (40 mg, 0.28 mmol) and triethylamine (100 mg, 1 mmol) were dissolved in 10 mL of acetonitrile, and dichloride **4** (60 mg, 0.25 mmol) was added with stirring at room temperature under an argon atmosphere. The reaction was allowed to proceed for 15 h at reflux. The reaction mixture was poured into 50 mL of water and extracted with benzene. The benzene layer was washed several times with water, dried (Na_2SO_4), and evaporated to give a yellow solid. The solid was chromatographed on silica using hexane–benzene to give dichloride **4** as colorless needles (25 mg, 42%), mp 157–158 °C, and dibenzotetrathiafulvalene (**2**) as yellow crystals (35 mg, 47%), mp 232–234 °C.

2-Dichloromethylene-1,3-dithiole (10). Disodium *cis*-ethenedithiolate (140 mg, 1.0 mmol) was dissolved in 10 mL of dimethylformamide. The solution was stirred at room temperature under an argon atmosphere, and tetrachloroethylene (510 mg, 3.0 mmol) was added dropwise. The reaction was allowed to proceed for 4 h at room temperature, and then the solution was poured into 30 mL of water and the mixture was extracted with benzene. The benzene layer was washed several times with water, dried (Na_2SO_4), and concentrated to give a dark brown oil. Chromatography on basic (I) alumina (hexane) gave 2-dichloromethylene-1,3-dithiole (**10**) as slightly yellow needles (80 mg, 42%), mp 55–58 °C; NMR δ 6.35 (s); mass spectrum *m/e* (rel intensity) 186 (74), 184 (100), 149 (62), 126 (32). This compound was not sufficiently stable to obtain an elementary analysis. It also decomposed readily on plates of silica gel or acid alumina, giving an initially colorless spot which turned blue and finally yellow.

Reaction of 2-Dichloromethylene-1,3-dithiole (10) with o-Benzenedithiol (1). *o*-Benzenedithiol (50 mg, 0.35 mmol), dichloride **10** (40 mg, 0.22 mmol), and triethylamine (100 mg, 1.0 mmol) were dissolved in 10 mL of acetonitrile. The solution was stirred for 15 h at reflux under an argon atmosphere. The reaction mixture was poured into 30 mL of water and extracted with benzene. The benzene layer was washed several times with water, dried (Na_2SO_4), and evaporated to give a brown oil, which was chromatographed on a dry silica column (hexane–benzene) to give yellow crystals of dibenzotetrathiafulvalene (**2**, 20 mg, 30%), mp 232–234 °C.

Reaction of Tetrakis(carbomethoxy)tetrathiafulvalene (12) with an Excess of o-Benzenedithiol (1). Tetraester **12**[10] (220 mg, 0.5 mmol), *o*-benzenedithiol (355 mg, 2.5 mmol), and triethylamine (505 mg, 5.0 mmol) were dissolved in 10 mL of acetonitrile. The solution was stirred for 15 h at reflux under an argon atmosphere. The reaction mixture was poured into 100 mL of water and extracted with benzene. The benzene layer was washed several times with water, dried (Na_2SO_4), and evaporated to give a yellow solid. Recrystallization from benzene gave yellow plates of dibenzotetrathiafulvalene (**2**, 140 mg, 92%), mp 231–233 °C.

Reaction of Tetraester 12 with an Equimolar Amount of o-Benzenedithiol (1). Tetraester **12** (220 mg, 0.5 mmol), *o*-benzenedithiol (75 mg, 0.5 mmol), and triethylamine (100 mg, 1.0 mmol) were dissolved in 10 mL of acetonitrile. The solution was stirred for 15 h at reflux under an argon atmosphere. The reaction mixture was poured into 50 mL of water and extracted with benzene. Workup as above, followed by chromatography on a dry silica column (hexane–benzene), gave yellow crystals of dibenzotetrathiafulvalene (**2**, 10 mg, 7%, mp 232–234 °C) and the reddish-brown diester **13** (35 mg, 19%). The latter solid was recrystallized from methanol to give reddish-brown needles (25 mg), mp 171–173 °C (lit.[6] 171–173 °C), identical (IR, mass spectrum) with authentic material.[6]

Acknowledgment. This work was supported by the National Science Foundation MRL program under Grant DMR 76-00678.

Registry No.—**1**, 17534-15-5; **2**, 24648-13-3; **4**, 64188-91-6; **6**, 17934-70-2; **10**, 64188-90-5; **12**, 26314-39-6; **13**, 62921-53-3; tetrachloroethylene, 127-18-4.

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Photochemical Reactions of N,N-Disubstituted α-Oxoamides

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Received July 18, 1977

Photochemical reactions of α-oxoamides having various substituents have been studied. Irradiation of *N,N*-dialkyl-α-oxoamides (**1b–d,h**) in methanol yielded the corresponding oxazolidin-4-ones (**2b–d,h**), as main products, while that of *N,N*-dibenzyl-α-oxoamides (**1e** and **1i**) in an aprotic solvent gave the corresponding β-lactams (**3e** and **3j**) predominantly. N-Substituted benzoylformanilides (**1k** and **1l**) afforded type II elimination products on irradiation. Mechanisms of these reactions have also been studied.

Photochemical reactions of α-dicarbonyl compounds such as α-diketones and α-oxoesters have been studied extensively.[1,2] However, those of α-oxoamides have received little attention. Akermark and Johanson investigated the photochemical reaction of an α-oxoamide **1a** and some related cyclic α-oxoamides in relation to their studies on penicillin chemistry, and reported that irradiation of **1a** yielded an oxazolidin-4-one **2a** as a major product accompanied by a small amount of a β-lactam **3a** (Scheme I).[3] Their studies were limited to these cyclic amides, and the mechanism for the formation of the unexpected product **2a** has not been clear.

Recently, we reported the photocyclization of α,β-unsaturated amides to β-lactams.[4] These unsaturated amides are isoelectronic with α-oxoamides. This fact and the absence of a systematic investigation on the photochemistry of α-oxoamides prompted us to study the photochemical reactions of these amides. In this paper, we wish to report on the photochemical reactions of α-oxoamides having various substituents, the solvent effects on the reactions, and the mechanism for the formation of the photoproducts.

Pyruvamides. When *N,N*-diethylpyruvamide (**1b**) in methanol was irradiated in a Pyrex vessel under argon with a high-pressure mercury lamp, 2,5-dimethyl-3-ethyloxazolidin-4-one (**2b**) was obtained in a quantitative yield. When an aprotic solvent such as benzene or acetonitrile was used, the yield of **2b** was poorer (56% in benzene and 45% in acetonitrile) and many unidentified by-products were produced. In all cases, analyses of the reaction mixtures by the IR spectra confirmed the absence of β-lactams. Irradiation of *N,N*-di-*n*-propylpyruvamide (**1c**) and *N,N*-diisopropylpyruvamide (**1d**) in methanol also afforded the corresponding oxazolidin-4-ones **2c** and **2d** almost quantitatively.

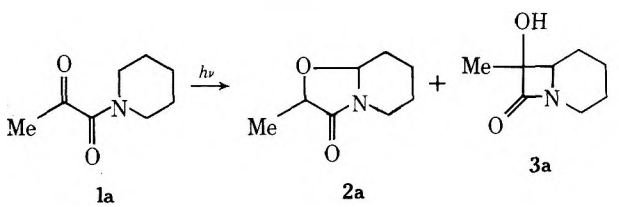
On the other hand, when *N,N*-dibenzylpyruvamide **1e** was irradiated in an aprotic solvent, 1-benzyl-3-hydroxy-3-methyl-4-phenylazetidin-2-one (**3e**) was obtained almost quantitatively. Irradiation of **1e** in methanol gave an oxazolidin-4-one **2e** (78%) as a main product accompanied by small amounts of **3e** (17%). Photochemical reaction of N-substituted pyruvanilides **1f** and **1g** showed similar solvent dependence (see Table I; Scheme II).

Benzoylformamides. Photolysis of *N,N*-diethylbenzoylformamide (**1h**) in methanol gave an oxazolidin-4-one **2h** as a main product, while that in benzene afforded **2h** in a lower yield. *N,N*-Diisopropylbenzoylformamide (**1i**) also gave an oxazolidin-4-one (**2i**) predominantly. However, a small amount of methyl mandelate (in methanol) and mandelanilide (in benzene) was produced in this case.

On the other hand, *N,N*-dibenzylbenzoylformamide (**1j**) yielded a β-lactam **3j** exclusively, both on irradiation in benzene and methanol.

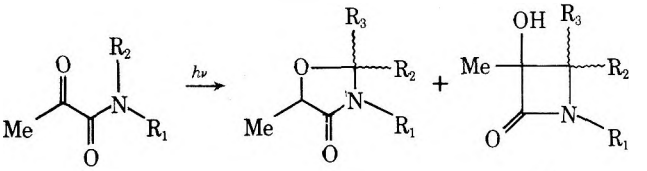
Finally, N-substituted benzoylformanilides **1k** and **1l** showed somewhat different photochemical behavior from other α-oxoamides. Irradiation of these anilides gave methyl

Scheme I



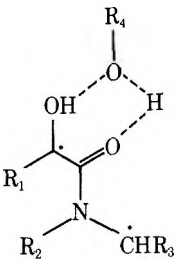
1a **2a** **3a**

Scheme II

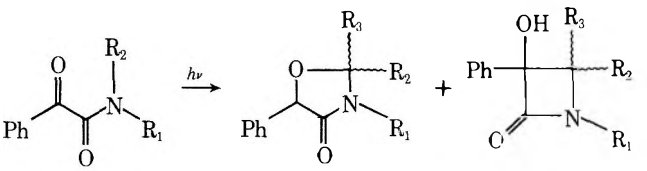


1 **2** **3**

b, $R_1 = R_2$ = Et — b, R_1 = Et; R_2 = Me; R_3 = H
c, $R_1 = R_2$ = *n*-Pr — c, R_1 = *n*-Pr; R_2 = Et; R_3 = H
d, $R_1 = R_2$ = *i*-Pr — d, R_1 = *i*-Pr; $R_2 = R_3$ = Me
e, $R_1 = R_2 = CH_2Ph$ — e, $R_1 = CH_2Ph$; R_2 = Ph; R_3 = H
f, R_1 = Et; R_2 = Ph — f, R_1 = Ph; R_2 = Me; R_3 = H
g, $R_1 = CH_2Ph$; R_2 = Ph — g, $R_1 = R_2$ = Ph; R_3 = H

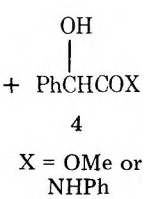


Scheme III



1 **2** **3**

h, $R_1 = R_2$ = Et — h, R_1 = Et; R_2 = Me; R_3 = H
i, $R_1 = R_2$ = *i*-Pr — i, R_1 = *i*-Pr; $R_2 = R_3$ = Me
j, $R_1 = R_2 = CH_2Ph$ — j, $R_1 = CH_2Ph$; R_2 = Ph; R_3 = H
k, R_1 = Et; R_2 = Ph — k, R_1 = Ph; R_2 = Me; R_3 = H
l, $R_1 = CH_2Ph$; R_2 = Ph — l, $R_1 = R_2$ = Ph; R_3 = H



4

X = OMe or NHPh

0022-3263/78/1943-0419$01.00/0

Table I. Photochemical Reaction of Pyruvamides

Reactant	Registry no.	Solvent	Yields, % 2	3
1b	22381-21-1	MeOH	100	*a*
1b		C_6H_6	56	*a*
1b		MeCN	45	*a*
1c	38382-90-0	MeOH	~100	*a*
1d	64201-02-1	MeOH	~100	*a*
1d		C_6H_6	86	*a*
1e	64201-00-9	MeOH	78	17
1e		C_6H_6	*a*	94
1f	61110-51-8	MeOH	58	*b*
1f		C_6H_6	*b*	46
1g	64201-20-3	MeOH	13	40
1g		C_6H_6	*a*	~100

[a] Not detected. [b] Trace.

Table II. Photochemical Reaction of Benzoylformamides

Reactant	Registry no.	Solvent	Yields, % 2	3	4
1h	34906-86-0	MeOH	73[b]	*a*	*a*
1h		C_6H_6	24[b]	7[b]	*a*
1i	51804-83-2	MeOH	58	22	16[c]
1i		C_6H_6	62	*e*	29[d]
1j	40991-79-5	MeOH	*a*	86	*a*
1j		C_6H_6	*a*	~100	*a*
1k	64201-19-0	MeOH	11	5	36[c]
1k		C_6H_6	14	12	34[d]
1l	64201-18-9	MeOH	*a*	27	35[c]
1l		C_6H_6	*a*	40	24[d]

[a] Not detected. [b] Not completely purified. [c] Methyl mandelate. [d] Mandelanilide. [e] Trace.

mandelate and mandelanilide as major products (see Scheme III).

Mechanism. The formation of the β-lactam, methyl mandelate, and mandelanilide can be explained in terms of a type II photoprocess. A biradical **5** is formed initially by γ-hydrogen abstraction by the ketone carbonyl oxygen. Cyclization of the biradical yields the lactam **3**, while C–N bond cleavage of it affords a hydroxy ketene **6** and an imine **7**. Addition of methanol to **6** gives methyl mandelate, and that of aniline which is formed by hydrolysis of **7** yields mandelanilide.[5] A similar reaction of ethyl benzoylformate to methyl mandelate has been reported by Huyser and Neckers.[2c] Intermediacy of the hydroxyketene **6** in the formation of mandelanilide was confirmed as follows. When **1k** in benzene was irradiated in the presence of an excess of *p*-toluidine, mandel-*p*-toluidide was produced instead of mandelanilide.

The formation of the oxazolidin-4-one (**2**) can be explained as shown in Scheme V. The biradical **5** undergoes 1,4-hydrogen migration to yield another biradical **8**. The biradical cyclizes to an enol **9** which ketonizes to give **2**. Analogous 1,4-hydrogen migration in photocyclization of α-diketones has been reported.[6] Some evidence in support of the intermediacy of the enol **9** was obtained from experiments using methanol-d_1. When a solution of **1b** in methanol-d_1 was irradiated, a deuterated product (**2b**-d_1) was obtained in a quantitative yield. On the other hand, the formation of **2b**-d_1 was not observed when a solution of **2b** in methanol-d_1 was irradiated or heated to 150 °C. An alternative path b, which involves hydrogen abstraction by the amide carbonyl oxygen through a five-membered transition state followed by rotation of the C–N bond, seems to be improbable because (a) reports on intramolecular hydrogen abstraction by an amide carbonyl group are few[7] and (b) intramolecular hydrogen abstraction through a five-membered transition state is the rarely observed process (Schemes IV and V).[8]

Solvent Effects. The formation of the oxazolidin-4-one **2** is apparently enhanced by alcoholic solvents. The photocyclization of **1b** to **2b** proceeded quantitatively in isopropyl or *tert*-butyl alcohol as in the case of methanol. Irradiation of **1b** in benzene containing 5% of methanol or in acetonitrile containing 5% of water gave the same result. It is well known that alcohols, water, and pyridine enhance a type II reaction of ketones by suppressing reverse hydrogen transfer in the biradical intermediate.[9] However, addition of pyridine to a benzene solution of **1b** showed no influence upon the photoreaction, and the yield of **2b** was still poor as in the case of a benzene solution. These results suggest that the alcohols or water play some roles in the 1,4-hydrogen migration step. The migration might proceed intermolecularly in hydroxylic solvents as shown below.

Substituents Effects. Substituents which stabilize the 1,4-biradical **5** seem to enhance the formation of the β-lactam **3**. Thus, *N,N*-Dibenzyl-α-oxoamides **1e** and **1j** gave the lactams **3e** and **3j** almost quantitatively on irradiation in an aprotic solvent. Furthermore, irradiation of *N,N*-dialkylbenzoylformamide **1h** and **1i** gave some amounts of the lactam **3h** and **3i**, while *N,N*-dialkylpyruvamide **1b** and **1d** did not give the corresponding β-lactams. Stabilization of the biradical **5** is presumed to make the 1,4-hydrogen migration inefficient.

Quantum Yields. The quantum yield for the cyclization of **1b** (oxazolidinone formation) was 0.66 in methanol. The reaction was sensitized by 4-methoxyacetophenone ($\Phi = 0.70$, $E_T = 72$ kcal) and less efficiently by 4-aminoacetophenone ($\Phi = 0.23$, $E_T = 65$ kcal), but not by Michler ketone ($E_T = 62$ kcal) or 4-phenylacetophenone ($E_T = 61$ kcal). On the other hand, the quantum yield for the reaction of **1j** (β-lactam formation) was 0.21 in benzene. The photoreaction was also sensitized by 4-methoxyacetophenone ($\Phi = 0.35$) but very inefficiently by 2-acetonaphthone ($\Phi = 0.04$, $E_T = 59$ kcal).

The above results indicate that the triplet states of **1b** and **1j** are reactive. However, both reactions were not quenched by high concentrations (1 M) of 1,3-pentadiene. This fact suggests that the photoreactions of **1b** and **1j** involve either the triplet reaction faster than bimolecular quenching or the singlet reaction faster than intersystem crossing.

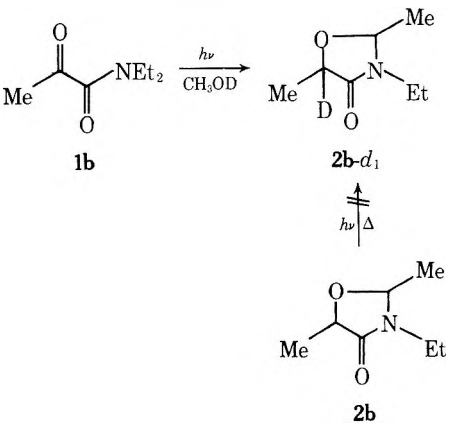
Experimental Section

All melting and boiling points were uncorrected. IR and NMR spectra were obtained on Hitachi EPI and R-20 spectrometers, respectively. A Ushio 450-W high-pressure mercury lamp was used as an irradiation source.

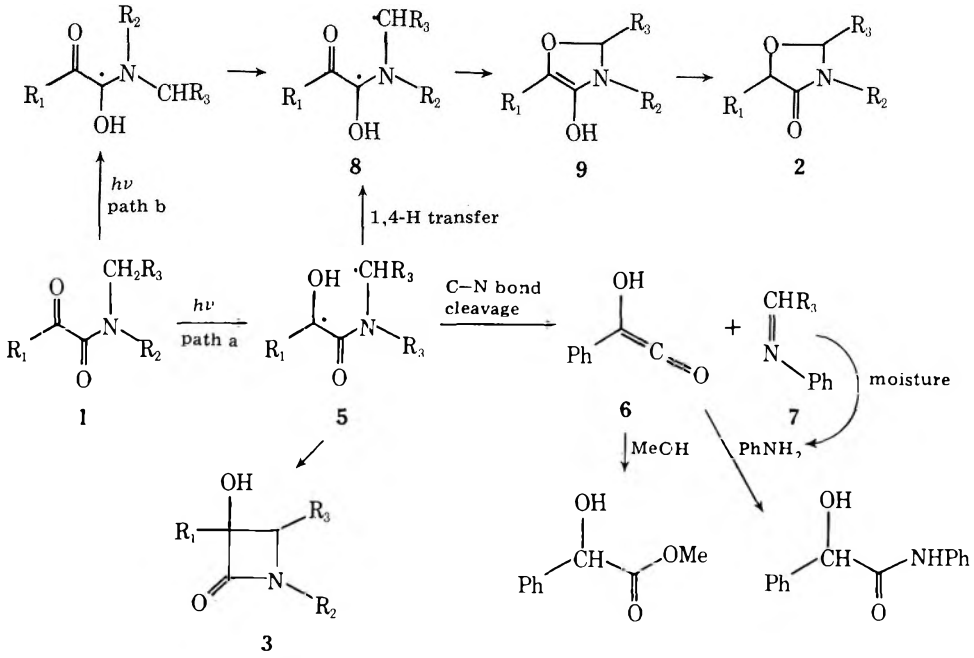
Materials. The oxoamides **1b–1l** were prepared according to the method in the literature.[10]

General Procedure for Photoreactions of α-Oxoamides. A

Scheme IV



Scheme V



solution of the α-oxoamide 1 (1%) was irradiated in a Pyrex vessel under argon with a high-pressure mercury lamp for 10–20 h. After removal of the solvent, the residue was chromatographed on silica gel. Elution with benzene–ethyl acetate afforded the photoproducts.

2,5-Dimethyl-3-ethyloxazolidin-4-one (2b): bp 60–65 °C (bath temp)/5 Torr; IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.42 (d, J = 7.5 Hz, 3 H, 5-CH_3), 1.45 (d, J = 5.5 Hz, 3 H, 2-CH_3), 3.75 (q of AB q, J_q = 7.5 Hz, J_{ABq} = 13 Hz, 2 H, CH_2), 4.25 (d of q, J_d = 1.5 Hz[11], J_q = 7.5 Hz, 1 H, 5-H), 5.18 (d of q, J_d = 1.5 Hz,[11] J_q = 5.5 Hz, 1 H, 2-H).

Anal. Calcd for $C_7H_{13}O_2N$: C, 58.71; H, 9.15; N, 9.78. Found:[12] C, 58.27; H, 9.21; N, 9.62.

5-Deuterio-2,5-dimethyl-3-ethyloxazolidin-4-one (2b-d_1): IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.42 (s, 3 H, 5-CH_3), 1.45 (d, J = 5.5 Hz, 3 H, 2-CH_3), 3.37 (q of AB_q, J_q = 7.5 Hz, J_{ABq} = 13 Hz, 2 H, CH_2), 5.18 (q, J = 5.5 Hz, 1 H, 2-H).

2-Ethyl-5-methyl-3-*n*-propyloxazolidin-4-one (2c): bp 90–95 °C (bath temp)/5 Torr; IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (t, J = 7 Hz, 6 H, two CH_2CH_3), 1.43 (d, J = 7 Hz, 3 H, 5-CH_3), 1.5–2.0 (m, 4 H, two CH_2), 3.24 (t of AB q, J_t = 8 Hz, J_{ABq} = 14 Hz, 2 H, N-CH_2), 4.31 (d of q, J_d = 1.8 Hz, J_q = 7 Hz, 1 H, 5-H), 5.09 (m, 1 H, 2-H).

Anal. Calcd for $C_9H_{17}O_2N$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.86; H, 10.15; N, 8.18.

2,2,5-Trimethyl-3-isopropyloxazolidin-4-one (2d): mp 34–36 °C; IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.27–1.37 (five CH_3), 3.30 (sep, J = 7 Hz, 1 H, N-CH), 4.11 (q, J = 7 Hz, 1 H, 5-H).

Anal. Calcd for $C_9H_{17}O_2N$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.78; H, 9.84; N, 8.26.

3-Benzyl-5-methyl-2-phenyloxazolidin-4-one (2e): bp 140–150 °C (bath temp)/5 Torr; IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (d, J = 7 Hz, 3 H, CH_3), 3.40 and 4.87 (AB q, J = 15 Hz, 2 H, CH_2), 4.30 (br q, J = 7 Hz, 1 H, 5-H), 5.55 (br s, 1 H, 2-H), 6.87–7.60 (m, 10 H, aromatic protons).

Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.42; H, 6.47; N, 5.26.

1-Benzyl-3-hydroxy-3-methyl-4-phenylazetidin-2-one (3e): mp 135.5–137 °C; IR (KBr) 3350, 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (s, 3 H, CH_3), 3.43 (s, 1 H, OH), 3.80 and 4.86 (AB q, J = 15 Hz, 2 H, CH_2), 4.28 (s, 1 H, 4-H), 6.91–7.51 (m, 10 H, aromatic protons).

Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.36; H, 6.41; N, 5.17.

2,5-Dimethyl-3-phenyloxazolidin-4-one (2f): mp 106–109 °C; IR (KBr) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (d, J = 5.5 Hz, 3 H, 2-CH_3), 1.53 (d, J = 6.5 Hz, 3 H, 5-CH_3), 4.42 (d of q, J_d = 1.5 Hz, J_q = 6.5 Hz, 1 H, 5-H), 5.70 (d of q, J_d = 1.5 Hz, J_q = 5.5 Hz, 1 H, 2-H), 7.10–7.50 (m, 5 H, aromatic protons).

Anal. Calcd for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.89; N, 7.47.

3,4-Dimethyl-3-hydroxy-1-phenylazetidin-2-one (3f): mp 141–142 °C; IR (KBr) 3340, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (d, J = 7 Hz, 3 H, 4-CH_3), 1.47 (s, 3 H, 3-CH_3), 4.12 (q, J = 7 Hz, 1 H, 4-H), 7.20–7.40 (m, 5 H, aromatic protons).

Anal. Calcd for $C_{11}H_{13}O_2N$: C, 69.09, H, 6.85; N, 7.33. Found: C, 68.70; H, 6.78; N, 7.04.

2,3-Diphenyl-5-methyloxazolidin-4-one (2g): mp 97–98 °C; IR (KBr) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (d, J = 7 Hz, 3 H, CH_3), 4.58 (q, J = 7 Hz, 1 H, 5-H), 6.41 (s, 1 H, 2-H), 7.19 and 7.33 (each s, each 5 H, aromatic protons).

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.09; H, 5.95; N, 5.55.

1,4-Diphenyl-3-hydroxy-3-methylazetidin-2-one (3g): mp 153–154 °C; IR (KBr) 3320, 1712 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 3 H, CH_3), 3.04 (s, 1 H, OH), 4.90 (s, 1 H, 4-H), 6.85–7.43 (m, 10 H, aromatic protons).

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.94; H, 5.84; N, 5.54.

3-Ethyl-2-methyl-5-phenyloxazolidin-4-one (2h) was not completely purified because it decomposed on standing or distillation: IR (neat) 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.57 (d, J = 6 Hz, 3 H, 2-CH_3), 3.35 (m, 2 H, CH_2), 5.16 (br s, 1 H, 5-H), 5.35 (m, 1 H, 2-H), 7.15–7.45 (m, 5 H, aromatic protons).

1-Ethyl-3-hydroxy-4-methyl-3-phenylazetidin-2-one (3h) did not crystallize and was not completely purified: IR (neat) 3350, 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (d, J = 6 Hz, 3 H, 4-CH_3), 1.13 (t, J = 7 Hz, 3 H, CH_2CH_3), 3.22 (m, 2 H, CH_2), 3.82 (q, J = 6 Hz, 1 H, 4-H), 7.26 (s, 5 H, aromatic protons).

2,2-Dimethyl-3-isopropyl-5-phenyloxazolidin-4-one (2i) was not completely purified because it was readily oxidized on standing to give a peroxide whose structure is not clear at present: IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.39 and 1.49 (each d, each 3 H, J = 4 Hz, isopropylmethyls), 1.52 and 1.55 (each s, each 3 H, 3-Me_2), 3.37 (m, 1 H, N-CH), 5.16 (s, 1 H, 5-H), 7.20–7.63 (m, 5 H, aromatic protons). The peroxide showed a positive KI–starch test: mp 145–146 °C; IR (KBr) 3175, 1695 cm^{-1}. Anal. Calcd for $C_{14}H_{19}O_2N{\cdot}O_2$: C, 63.38; H, 7.21; N, 5.28. Found: C, 63.54; H, 7.16; N, 5.27.

4,4-Dimethyl-3-hydroxy-1-isopropyl-3-phenylazetidin-2-one (3i): mp 140–141 °C; IR (KBr) 3250, 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (s, 3 H, 4-CH_3 cis to Ph), 1.25 (s, 3 H, 4-CH_3 trans to Ph), 1.41 (d, J = 7 Hz, 6 H, isopropylmethyls), 3.58 (sep, J = 7 Hz, 1 H, N-CH), 4.50 (s, 1 H, OH), 7.28 (s, 5 H, aromatic protons).

Anal. Calcd for $C_{14}H_{19}O_2N$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.31; H, 8.28; N, 5.91.

3,4-Diphenyl-1-benzyl-3-hydroxyazetidin-2-one (3j): mp 100–102 °C; IR (KBr) 3325, 1730 cm^{-1}; NMR ($CDCl_3$) δ 3.86 and 4.94 (AB q, J = 15 Hz, 2 H, CH_2), 3.95 (s, 1 H, OH), 4.54 (s, 1 H, 4-H), 6.90–7.50 (m, 10 H, aromatic protons).

Anal. Calcd for $C_{22}H_{19}O_2N$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.34; H, 5.82; N, 4.19.

3,5-Diphenyl-2-methyloxazolidin-4-one (2k): mp 105.5–107 °C; IR (KBr) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (d, J = 5 Hz, 3 H, CH_3),

5.35 (br s, 1 H, 5-H), 5.91 (br q, J = 5 Hz, 1 H, 2-H), 7.00–7.70 (m, 10 H, aromatic protons).

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.03; H, 6.00; N, 5.55.

1,3-Diphenyl-3-hydroxy-4-methylazetidin-2-one (3k): mp 175–176.5 °C; IR (KBr) 3300, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (d, J = 6 Hz, 3 H, CH_3), 4.03 (s, 1 H, OH), 4.36 (q, J = 6 Hz, 1 H, 4-H), 6.95–7.55 (m, 10 H, aromatic protons).

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.98; H, 6.01; N, 5.51.

1,3,4-Triphenyl-3-hydroxyazetidin-2-one (31): mp 172–174 °C; IR (KBr) 3550, 3300, 1735, 1715 cm^{-1}; NMR ($CDCl_3$) δ 5.19 (s, 1 H, 4-H), 6.90–7.72 (m, 15 H, aromatic protons).

Anal. Calcd for $C_{21}H_{17}O_2N$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.83; H, 5.24; N, 4.42.

Quantum Yield Determinations. Benzophenone–benzhydrol actinometry was used for quantum yield determination. The 313-nm line was isolated with a filter solution containing 0.002 M potassium chromate in 5% aqueous potassium carbonate. Samples (0.10 M solution) in Pyrex tubes were degassed to ca. 10^{-3} mm in three freeze–thaw cycles and sealed. The samples were irradiated individually in succession. Photolyses were carried out to 30–50% conversion. The degree of reaction was determined by NMR spectroscopy. Concentrations of the sensitizer were adjusted so that 5% or less of the incident light was absorbed by the oxoamides (**1b** and **1j**).

Acknowledgment. We thank Dr. Choji Kashima for his useful suggestions. Partial financial support by a Matsunaga Research Grant is gratefully acknowledged.

Registry No.—**2b,** 64201-17-8; **2b-d_1,** 64201-16-7; **2c,** 64201-15-6; **2d,** 64201-14-5; **2e,** 64201-13-4; **2f,** 64201-12-3; **2g,** 64201-11-2; **2h,** 64201-10-1; **2i,** 64201-09-8; **2k,** 64201-08-7; **3e,** 64201-07-6; **3f,** 64201-06-5; **3g,** 64201-05-4; **3h,** 64201-04-3; **3c,** 64201-03-2; **3j,** 64201-01-0; **3k,** 64200-99-3; **3l,** 64201-21-4.

References and Notes

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Regio- and Stereoselectivity of the Formation of Halohydrins from 3-Methyl- and 3-*tert*-Butylcyclohexene and from the Corresponding Epoxides

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Received June 14, 1977

In order to explain large variations in product regio- and stereochemistry observed in several types of ionic additions to cycloalkenes involving different reagents, the product compositions obtained in some reactions leading from 3-methyl- and 3-*tert*-butylcyclohexene to chlorohydrins, bromohydrins, and bromoacetoxy derivatives have been investigated in detail. Whereas with *N*-chlorosuccinimide, preformed HOBr, or CH_3COOBr electrophilic attack was nonstereoselective for the methyl and anti stereoselective for the *tert*-butyl derivative, with NBS a high syn stereoselectivity was observed for the attack by electrophilic bromine, which indicated that repulsive steric effects operating during the nucleophilic step should be the main product-determining factor in the latter case, and that this step should be the rate-limiting one. Support of this hypothesis was brought by the reactions of the corresponding epoxides with HBr and HCl, since the observed regioselectivities of these reactions, which can be taken as models for the nucleophilic opening of the halonium intermediates of the electrophilic additions to olefins, are in agreement with those deduced from the product compositions of the latter reactions.

As a part of a research program concerning the influence of steric, polar, and conformational effects on electrophilic additions involving different types of reagents and different mechanisms,[1-4] we undertook a comparative product and kinetic study of additions to 3-alkylcyclohexenes involving epihalonium ion intermediates and of the ring-opening reactions of diastereoisomeric couples of 3-alkyl-1,2-epoxycyclohexanes, which can be taken as models for the nucleophilic steps of the additions. A methyl and a *tert*-butyl group were chosen as alkyl substituents having, respectively, a relatively small and very large size. In this paper, we report the results of the product study.[5]

Results

3-*tert*-Butylcyclohexene Derivatives. As reported by Richer,[6] the epoxidation of 3-*tert*-butylcyclohexene (**1a**) with peroxyacids yielded a 90:10 mixture of the trans and cis epoxides **2a** and **3a.** Opening of this mixture with hydrogen bromide afforded three isomeric bromohydrins, which were separated by column chromatography. The most abundant compound was identified as the diequatorial bromohydrin **5c** on the basis of its NMR spectrum[7] and of its conversion back to **2a** by treatment with base. The other two isomers were trans diaxial bromohydrins, as shown by the narrow signals, due to equatorial protons α to bromine and hydroxyl, appearing in the medium-field part of their NMR spectra; they were identified as **4c** and **6c** by conversion, respectively, into the epoxides **2a** and **3a.**

This method was convenient for the preparation of the pure trans epoxide **2a,** since the separation of bromohydrin **5c** from

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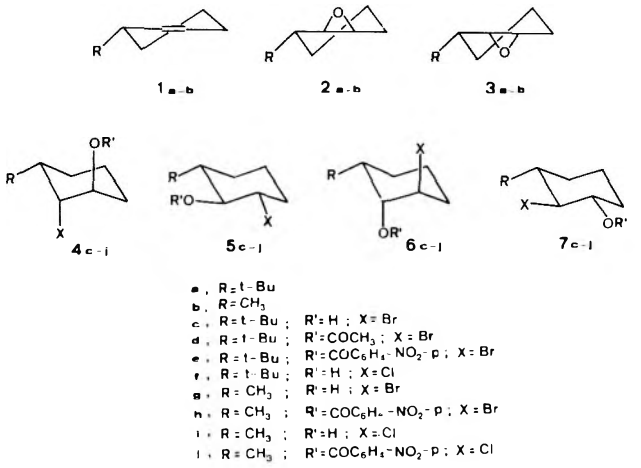
Table I. Product Distributions for Additions to 3-*tert*-Butylcyclohexene[a]

Reagent	Solvent	Products Type	Distribution, % 4	5	6	7
NBS	Me_2SO–H_2O (95:5)	c	78	4	3	15
NBS	H_2O	c	54	4	19	23[b]
NBA	Dioxane–H_2O (7:3)	c	81	3	4	12
NBA	Dioxane–0.2 N aq $HClO_4$ (7:3)	c	76	4	5	15
HOBr (aq)	Dioxane	c				c
AcOBr	CCl_4	d	13	2	9	76
NCS	H_2O	f	14	3	25	58[d]

[a] For experimental conditions, see Experimental Section. [b] About 30% of trans dibromides were also formed. Complete thermal isomerization of the diequatorial into the diaxial dibromo adduct under the GLC conditions prevented the determination of their ratio (see ref 25). [c] An accurate determination was prevented by overlap of the peak of **5** with an unidentified by-product in the chromatogram. However, **7** was evaluated to amount to more than 50% of the total products. [d] Diaxial and diequatorial dichlorides (about 35%) in a 4:6 ratio were also formed.



its isomers was easy, but not for that of the diastereoisomer **3a,** because of the small amount of **6c** that could be isolated. In the search for a stereoselective route to **3a,** the addition of the elements of hypobromous acid to **1a** followed by cyclization of the resulting bromohydrins were investigated. This method has been frequently used to obtain the diastereoisomeric epoxide formed in lower yield by direct epoxidation.[8] In contrast with the expectation, bromohydrin **4c,** having the hydroxyl trans to the *tert*-butyl group, was however isolated as the main product of the reactions of **1a** by the usual methods,[9–11] both with *N*-bromosuccinimide (NBS) in Me_2SO–water and with *N*-bromoacetamide (NBA) in dioxane–water, and this preference for attack by electrophilic bromine syn to the *tert*-butyl group was confirmed by the fact that base-promoted cyclization of the crude bromohydrin mixtures gave an excess of epoxide **2a.**

However, when the addition to **1a** was carried out with an aqueous solution of preformed hypobromous acid, the main product was **7c** (identified by NMR[7]). Its isolation by column chromatography gave a low yield owing to decomposition and isomerization to **6c,** but cyclization of the crude addition mixture with potassium hydroxide gave the two epoxides **2a** and **3a** in a 20:80 ratio.

A 15:85 mixture of **2a** and **3a** was finally obtained by addition of preformed acetyl hypobromite to **1a** in carbon tetrachloride followed by refluxing of the resulting crude acetoxy bromo adducts **4d–7d** with potassium carbonate in aqueous methanol. Opening of the latter mixture of epoxides with hydrogen bromide and column chromatography afforded a fairly good yield of bromohydrin **6c,** the cyclization of which gave pure **3a.** Alternatively, **3a** was conveniently obtained by potassium carbonate treatment of the major product **7d,** formed in the acetoxybromination of **1a** and separated from the accompanying isomers **4d, 5d,** and **6d** by column chromatography.

Table II. Regioselectivity of Opening Reactions of 2a and 3a with Hydrogen Halides in CCl_4

Epoxide	Hydrogen halide	Products Type	4:5 ratio	6:7 ratio
2a	HBr	c	29:71	
2a	HCl	f	38:62	
3a	HBr	c		93:7
3a	HCl	f		93:7

Because of the very marked dependence of the steric course of the additions to **1a** on the reagent used as the source of positive bromine, complete stereo- and regioselectivity data were sought by direct GLC analysis of the addition products. The reaction of **1a** with *N*-chlorosuccinimide (NCS) in water was also investigated. This reaction proceeded conveniently at 90–100 °C.[12] The reference trans chlorohydrins **4f–7f** had already been described.[13] The product distributions found for the various addition reactions, as reported in Table I, confirm the largely different steric courses between the *N*-bromoamide-promoted reactions on one hand and the additions of HOBr or AcOBr on the other (Table I).

In contrast, no such difference was apparent in the steric course of the chlorohydrin formation by the NCS reaction, which was very similar to that reported for the addition of chlorine in the presence of aqueous sodium carbonate.[13]

For comparison purposes, the reaction of epoxides **2a** and **3a** with hydrogen bromide and chloride was also examined. The percentages of the two isomeric trans halohydrins formed from each epoxide are reported in Table II.

3-Methylcyclohexene Derivatives. The peroxyacid oxidation of 3-methylcyclohexene (**1b**) afforded about equal amounts of the diastereoisomeric epoxides **2b** and **3b,**[14] which could not be separated by the usual techniques. Opening of the mixture with hydrogen chloride and esterification of the formed trans chlorohydrins with *p*-nitrobenzoyl chloride gave, after several crystallizations, a *p*-nitrobenzoyl derivative previously isolated by Rickborn.[14] Structure and relative configuration shown in **6j** resulted from the NMR spectrum of this compound (Table III), the multiplicity and coupling constants of the δ 5.16 signal, due to the proton α to the ester group, clearly establishing a vicinal cis relationship between *p*-nitrobenzoyloxy and methyl substituents. This confirmed the cis configuration **3b** assigned on the basis of hydride reduction[14] to the epoxide obtained by potassium carbonate treatment of **6j.**

The trans-epoxide **2b,** which had never been obtained pure, was prepared by a similar cyclization of the bromohydrin

Table III. NMR Data of *p*-Nitrobenzoates of Halohydrins[a]

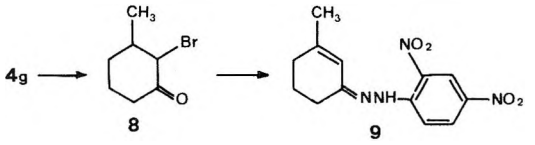
Compd	Registry no.	$-CH_3$ δ	$-CH_3$ J, Hz	>CHX δ	>CHX W	>CHX J, Hz	>CH-O- δ	>CH-O- W	>CH-O- J, Hz	$-C_6H_4NO_2$-p, δ
4h	64162-82-9	1.06 (d)	6.4	4.40 (t)		3.7	5.45 (m)	12		8.27 (s)
5h	64162-83-0	0.99 (d)	6.0	4.15 (m)	25		5.09 (t)		9.3	8.35 (s)
6h	64199-95-7	0.98 (d)	7.0	4.46 (m)	15		5.29 (d of d)		3.4, 5.2	8.30 (s)
7h	64199-96-8	1.23 (d)	6.0	3.80 (t)		10.3	5.22 (m)	25		8.27 (s)
4j	64162-84-1	1.09 (d)	6.7	4.25 (t)		3.9	5.37 (m)	12		8.30 (s)
5j	64162-85-2	1.00 (d)	6.0	4.02 (m)	25		5.05 (t)		9.8	8.35 (s)
6j	64199-97-9	0.99 (d)	6.7	4.31 (m)	14		5.16 (d of d)		3.4, 5.2	8.25 (s)
7j	64199-98-0	1.20 (d)	6.0	3.71 (t)		10.0	~5.1 (m)	*b*		8.25 (s)

[a] In $CDCl_3$. [b] Not measured owing to overlap with the signal at δ 5.16 of the contaminating isomer **6j**.

Table IV. Regioselectivity of Opening Reactions of 2b and 3b with Hydrogen Halides in $CHCl_3$

Epoxide	Hydrogen halide	Products Type	4:5 ratio	6:7 ratio
2b	HBr	**g**	64:36	
2b	HCl	**i**	62:38	
3b	HBr	**g**		90:10
3b	HCl	**i**		93:7

p-nitrobenzoate **4h**, easily obtained from the reaction of **1b** with NBS in Me_2SO–H_2O followed by esterification with *p*-nitrobenzoyl chloride and fractional crystallization. This established a trans relationship between hydroxyl and methyl groups in the parent bromohydrin formed as the main product of the NBS reaction. This product, isolated by column chromatography, was shown to have bromine vicinal to the methyl group (**4g**) by oxidation to bromo ketone **8** and subsequent dehydrobromination with 2,4-dinitrophenylhydrazine[15] to the known derivative **9**.[16]



The reaction of the trans-epoxide **2b** with hydrogen bromide yielded, besides **4g**, the alternative product of trans ring opening, **5g**, which was separated by column chromatography. Isomer **6g** was obtained from the similar opening of the cis-epoxide **3b**. The fourth bromohydrin (**7g**), formed in too small amount both in the NBS reaction of **1b** and in the hydrogen bromide opening of **3b**, was instead isolated as its *p*-nitrobenzoate from the reaction of preformed hypobromous acid with **1b** by a combination of column and thin-layer chromatography.

In a similar way, chlorohydrins **4i** and **5i** were isolated from the opening reactions of **2b** with hydrogen chloride, while **6i** was obtained from the cis-epoxide **3b**. The fourth isomer **7i** was not isolated in a pure state, but a mixture of **6i** and **7i** enriched in the latter isomer was separated by chromatography from the products of the reaction of **1b** with NCS in water.

Structures, relative configurations, and conformations of all bromohydrins **4g**–**7g** and chlorohydrins **4i**–**6i** were demonstrated or confirmed by the NMR spectra of their *p*-nitrobenzoates (Table III), on the basis of the multiplicity and coupling constants of the signals for the protons α to acyloxy and halogen.

Compounds **5** and **7** exhibited the expected triequatorial conformations, as shown by the high value[17] of the coupling constants of the protons α to the halogen and ester group between themselves and with the proton α to methyl. The low *J* values in the spectra of compounds **4** were consistent[17] with a high preference for conformations with equatorial methyl and axial halogen and ester group. In products **6**, instead, one of the coupling constants of the proton α to the *p*-nitrobenzoyloxy group was slightly higher than expected for an equatorial proton, probably because of some contribution to the conformational equilibrium by the alternative chair form with equatorial halogen and ester group and axial methyl.

Table V. Product Distributions for Additions to 3-Methylcyclohexene[a]

Reagent	Solvent	Products Type	Distribution, % 4	5	6	7
NBS	Me_2SO–H_2O (95:5)	**g**	77	5	11	7
NBS	H_2O	**g**	76	4	15	5
HOBr (aq)	Dioxane	**g**	47	3	33	17
NCS	H_2O	**i**	47	9	26	18

[a] For experimental conditions, see Experimental Section. Only traces of trans dihalides were formed in all these reactions.

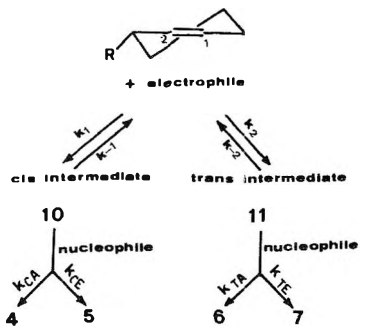
The percentages of the two isomeric halohydrins obtained by GLC analysis of the products of ring opening of **2b** and **3b** with hydrogen bromide and chloride are quoted in Table IV.

Finally, Table V shows the product distributions found in several addition reactions to **1b**. As in the additions to 3-*tert*-butylcyclohexene (**1a**), the formation of products of type **4** decreased, although less markedly, in favor of those of type **6** and **7** on passing from NBS to preformed HOBr and to NCS as the electrophilic reagents. These results excluded the possibility that HOBr, which could have been formed by hydrolysis of NBS or NBA, was the actual reactant in all *N*-bromoamide reactions of **1a** and **1b**, and rather pointed to a direct transfer of bromine from nitrogen to the double bond. In contrast, the similarity in the steric courses observed in the NCS–water and in the hypohalous acid reactions of both **1a** and **1b** suggested hydrolysis of NCS to HOCl before the electrophilic attack.

Discussion

Representative stereo- and regioselectivity data for additions to alkenes **1a** and **1b**, extracted from Tables I and V, are compared in Table VI.[18] The regioselectivity of the attack by the different nucleophiles (water, Me_2SO,[19] acetate) anti to the alkyl substituent, which is given by the **4:5** ratio, is always high and very similar for both alkenes under all examined conditions. Also, the regioselectivity of the syn attack, given by the **6:7** ratio, exhibits a fairly constant trend for each olefin, but is markedly affected by the size of the allylic substituent. Moreover, the observed trends are comparable to those found in the ring-opening reactions of epoxides **2** and **3** with hydrogen halides (Tables II and IV).[20] This analogy, which had been observed also with other cyclohexene derivatives bearing electron-withdrawing substituents,[1,4,21,22] strongly suggests

Scheme I



for all examined reactions two-step addition mechanisms in which bridged intermediates are formed in the electrophilic stage, the main factors affecting the regioselectivity of the subsequent nucleophilic attacks being similar to those operating in the ring opening of the corresponding epoxides.

Nucleophilic attack on the cis-intermediates **10** (Scheme I), as well as on cis-epoxides **3**, occurs preferentially at C(1) to give mainly the expected diaxial products (**4** from **10** or **6** from **3**). On the other hand, the formation of diaxial products **6** from the trans-intermediates **11**, or of **4** from the trans-epoxides **2**, involves a nucleophilic attack at C(2) which is subjected to a steric hindrance by the 3-alkyl substituent. When R is methyl, this attack is still slightly predominant (59–66%), but the alternative attack at C(1) to give diequatorial adducts (**7** from **11** or **5** from **2**) becomes favored, in spite of its unfavorable conformational requirements,[23] when R is a bulky *tert*-butyl group.

If one excludes the NBS reactions, the stereoselectivity data of Table VI, giving the relative contributions of intermediates **10** and **11** to the reaction pathways, show that in all additions to **1a** the trans-intermediate **11** is highly predominant, in accordance with a strong steric effect of the *tert*-butyl group during the electrophilic step, as observed also in the epoxidation of **1a** (90% anti attack), whereas no stereoselectivity in the formation of the two intermediates **10** and **11** is observed in the analogous reactions of **1b**, consistent with the lack of any steric effect by the allylic methyl group in the epoxidation of **1b**. All these data can be rationalized on the basis of the mechanism represented in Scheme I, if the formation of intermediates **10** and **11** is practically irreversible and their subsequent reactions to give products are a fast step (k_{CA}, k_{CE}, k_{TA}, $k_{TE} \gg k_1$, k_2, k_{-1}, k_{-2}; $k_2 > k_1$ for **1a** and $k_2 \simeq k_1$ for **1b**).

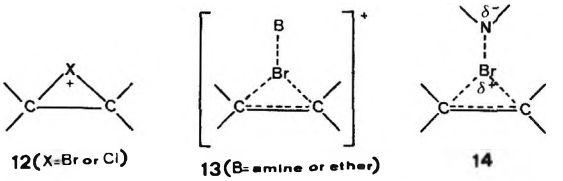
On the other hand, the stereoselectivities observed in the *N*-bromoamide reactions cannot be accounted for on the basis of the same mechanism, since it would imply that $k_1 > k_2$ for both **1a** and **1b**, in contrast with the anticipated retarding effect of the *tert*-butyl and with the expected absence of an accelerating effect by the methyl group on the rates of syn electrophilic attack. The product distributions observed in the latter reactions would be instead consistent with k_{CA}, k_{CE}, k_{TA}, $k_{TE} < k_1$, k_2, k_{-1}, k_{-2}; $k_{CA} + k_{CE} > k_{TA} + k_{TE}$; $k_{CA} \gg k_{CE}$; $k_{TA} > k_{TE}$ for **1b** and $k_{TE} > k_{TA}$ for **1a**. This implies that the electrophilic step be reversible and the cis intermediate **10** be more reactive than the trans intermediate **11**. The latter assumption is supported by the reactivity order found[24] for the hydrogen chloride opening reactions of epoxides **2** and **3**, the protonated forms of which, as previously mentioned, can be considered as fairly reliable models for the bridged intermediates **11** and **10**, respectively.

As far as the nature of the intermediates is concerned, there seems to be no reason for assuming structures different from epihalonium ions **12** (possibly as ion pairs with the appropriate anions) for all examined reactions which appear to proceed through a slow, irreversible electrophilic attack. However, the change in mechanism observed in the *N*-bromoamides reactions can be better explained assuming different bridged species as the intermediates formed in a reversible electrophilic step.

Table VI. Stereo- and Regioselectivities of Additions to 1a and 1b

Reagent	Olefin	Stereoselectivity 10:11	Regioselectivity 4:5	Regioselectivity 6:7
NBS (Me_2SO–H_2O)	**1a**	82:18	95:5	17:83
	1b	82:18	94:6	61:39
HOBr (aq) (dioxane)	**1a**	20:80	$4 \gg 5$	$6 \ll 7$
	1b	50:50	94:6	66:34
AcOBr (CCl_4)	**1a**	15:85	87:13	11:89
NCS (H_2O)	**1a**	17:83	82:18	30:70
	1b	56:44	84:16	59:41

Some time ago we proposed[25] that the bromination of compounds **1** with amine–bromine or ether–bromine complexes could occur through a pre-rate-determining equilibrium leading to species of type **13**, in which bromine is bonded both to the base and to the olefinic carbon atoms. A similar intermediate has been later invoked[26] for the bromochlorination of cyclopentadiene with amine–bromine–chloride



complexes. By analogy, we believe that the intermediates of the *N*-bromoamide reactions on olefins may be represented by species **14**, which, being formed rapidly and being conceivably less reactive than bromonium ions, may be subjected to slow rate- and product-determining nucleophilic attack. Similar conclusions have been independently inferred[27] from a study of the relative nucleophilicities of Me_2SO and methanol toward the intermediates formed in the reaction of olefins with bromine and *N*-bromoamides.

In conclusion, all available data indicate the possibility of two different stepwise mechanisms of anti addition to cyclohexene derivatives. In the first, more widely occurring one, the stereoselectivity is controlled during a slow electrophilic step and the regioselectivity during the subsequent nucleophilic steps. In the absence of specific interactions between substituents on the substrate and the electrophile,[4] this mechanism leads to product distributions which can be roughly foreseen on the basis of the stereoselectivity of the peroxyacid oxidation of the substrate and of the regioselectivity of the ring-opening reactions of the resulting diastereoisomeric epoxides. In the second mechanism, both the stereo- and the regioselectivity are instead controlled by steric, electronic, and conformational factors operating during a rate- and product-determining nucleophilic step, and the product distribution can be roughly anticipated on the basis of the relative reactivities of the diastereoisomeric epoxides arising from the substrate.[24] The latter mechanism, which has been proposed also for reactions of dihydropyran derivatives,[28] appears to be peculiar to the reactions of *N*-bromoamides (but not for *N*-chloroamides), iodine compounds,[29-32] amine–halogen and ether–halogen complexes, and to some oxymercuriation reactions.[33]

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were taken from CCl_4 solutions (except when differently stated) with a Jeol C-60 HL spectrometer using Me_4Si as

internal standard. GLC analyses were performed with a C. Erba Fractovap Model GV and a Perkin-Elmer Model F11 instrument. Neutral silica gel (Schuchardt, 150–300 μ) was always used for column chromatographies. Usual workup of reaction products involved extraction with a solvent (if necessary), washing with H_2O (10% Na_2CO_3 if acidic), drying with $MgSO_4$, and evaporation in vacuo (rotating evaporator). Petroleum ether refers to the fraction of boiling range 40–60 °C.

***t*-2-Bromo-*t*-3-*tert*-butyl-*r*-1-cyclohexanol (4c), *t*-2-Bromo-*t*-6-*tert*-butyl-*r*-1-cyclohexanol (5c), and *t*-2-Bromo-*c*-6-*tert*-butyl-*r*-1-cyclohexanol (6c). A.** A solution of **1a** (12 g, 0.086 mol) in $CHCl_3$ (120 mL) was treated dropwise under stirring at 0 °C with a 0.35 M $CHCl_3$ solution of peroxybenzoic acid (370 mL, 0.13 mol). After standing overnight at 4 °C, the solution was worked up as usual to give a liquid residue (8.8 g) consisting of epoxides **2a** and **3a** in a 90:10 ratio (GLC: 2-m glass column, 2.5-mm i.d., packed with 1% neopentyl glycol succinate on silanized Chromosorb W, 80–100 mesh; column 90 °C, evaporator and detector 200 °C, nitrogen flow 40 mL/min; relative rentention times 1.20:1).

A solution of this mixture in $CHCl_3$ (60 mL) was saturated with dry HBr and worked up after 30 min to give a residue (12.0 g) consisting of bromohydrins **4c, 5c,** and **6c**. A part of this mixture (9.5 g) was chromatographed over a 2.2 × 50 cm column of silica gel (76 g). Petroleum ether eluted pure **5c** (5.0 g) as an oil.[7]

Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.06; H, 8.14; Br, 33.98. Found: C, 50.98; H, 8.30; Br, 33.45.

Treatment of **5c** (0.30 g, 1.28 mmol) with phenyl isocyanate (0.165 g, 1.38 mmol) on a water bath for 30 min gave the phenylurethane, mp 127–128 °C (from petroleum ether).[7]

Anal. Calcd for $C_{17}H_{24}BrNO_2$: C, 57.62; H, 6.78; Br, 22.59. Found: C, 57.78; H, 6.80; Br, 22.26.

Elution with 98:2 petroleum ether–ethyl ether gave pure **6c** (0.5 g): mp 74–76 °C (from petroleum ether); NMR δ 0.98 [s, $-C(CH_3)_3$, 9 H], 2.16 (s, –OH, 1 H), 4.22 (two overlapping m, >CHOH and >CHBr, $W_{1/2}$ = 5.5 Hz, 2 H).

Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.06; H, 8.14; Br, 33.98. Found: C, 51.30; H, 7.98; Br, 34.26.

Further elution yielded pure **4c** (1.5 g): mp 70 °C (from petroleum ether); NMR δ 1.00 [s, $-C(CH_3)_3$, 9 H], 3.57 (s, –OH, 1 H), 4.11 (m, $W_{1/2}$ = 7.5 Hz, >CHOH or >CHBr, 1 H), 4.29 (m, $W_{1/2}$ = 7 Hz, >CHBr or >CHOH, 1 H).

Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.06; H, 8.14; Br, 33.98. Found: C, 51.05; H, 7.95; Br, 34.50.

B. *N*-bromoacetamide (3.3 g, 0.024 mol) was added to a solution of **1a** (3.0 g, 0.022 mol) in 7:3 dioxane–water (200 mL). After stirring for 1 h at room temperature, the reaction mixture was diluted with water and extracted with ether to yield 4.1 g of mixed bromohydrins **4c–7c.**

A sample of this mixture (0.2 g) was treated with 1 M ethanolic KOH (5 mL). After 30 min, dilution with water and extraction with ether gave epoxides **2a** and **3a** in a 84:16 ratio (GLC).

The remaining mixture was chromatographed on a 1.8 × 57 cm column of silica gel (110 g). Petroleum ether–ethyl ether (98:2 and 95:5) eluted in succession: **5c** (0.13 g), **6c** (0.15 g), mixtures of **4c, 6c,** and **7c** (0.18 g), and **4c** (2.2 g).

C. A solution of **1a** (3.0 g, 0.022 mol) in 95:5 Me_2SO–water (50 mL) was stirred with NBS (4.3 g, 0.024 mol) at room temperature for 1 h. Treatment as described under **B** gave a mixture of **4c–7c** (4.2 g).

The cyclization of a sample of this mixture with ethanolic KOH yielded epoxides **2a** and **3a** in a ratio of 82:18 (GLC).

D. A 0.1 M CCl_4 solution of acetyl hypobromite[34] (540 mL) was added dropwise at 0 °C to a solution of **1a** (6.9 g, 0.05 mol) in the same solvent (20 mL). After the addition was complete, the solution was stirred at 0 °C for 1 h and then washed with saturated aqueous $NaHSO_3$ and worked up. The residue (12.0 g) was dissolved in MeOH (400 mL), a solution of 13.5 g of K_2CO_3 in 40 mL of water was added, and the mixture was refluxed for 2 h with occasional shaking, then diluted with water, and extracted with ether. Distillation of the residue yielded a mixture of epoxides **2a** and **3a** (6.0 g), bp 85–90 °C (20 mm), in a 15:85 ratio (GLC).

Treatment of these epoxides (3.0 g) with dry HBr as reported under **A** gave a mixture of bromohydrins **4c–7c** (4.5 g), which was chromatographed on a 2.2 × 50 cm column of silica gel. Petroleum ether eluted **5c** (0.5 g), 99:1 petroleum ether–ethyl ether eluted **6c** (3.0 g), and 1:1 petroleum ether–ethyl ether yielded **4c** (0.2 g).

***t*-2-Bromo-c-3-*tert*-butyl-*r*-1-cyclohexanol (7c).** A 0.7 M aqueous solution of HOBr[35] (57 mL) was added dropwise to a stirred solution of **1a** (5.0 g, 0.036 mol) in dioxane (100 mL) at room temperature. After 30 min the reaction mixture was diluted with water and extracted with ether to afford 6.2 g of a residue, GLC of which revealed the prevailing presence of bromohydrin **7c,** besides isomers **4c, 5c, 6c,** trans dibromides, and other components.

Cyclization of a sample of this mixture (0.2 g) with 1 N ethanolic KOH gave **2a** and **3a** in a 20:80 ratio.

The remaining mixture was chromatographed on a 2.2 × 81 cm column of silica gel (120 g). Elution with petroleum ether gave small amounts of unreacted **1a,** *r*-1,*t*-2-dibromo-*t*-3-*tert*-butylcyclohexane,[36] and **5c** (0.4 g). Elution with 99:1 petroleum ether–ethyl ether yielded fractions containing **7c** and other components (0.7 g), and then pure **7c** (0.5 g) as an oil.[7]

Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.06; H, 8.14; Br, 33.98. Found: C, 51.19; H, 8.19; Br, 33.49.

p-Nitrobenzoate (**7e**): mp 116–118 °C (from EtOH).[7]

Anal. Calcd for $C_{17}H_{22}BrNO_4$: C, 53.13; H, 5.77; Br, 20.79. Found: C, 53.10; H, 5.66; Br, 20.60.

Further elution yielded various mixtures of **7c** and **6c,** pure **6c,** and other components. Bromohydrin **7c** was converted into **6c**[37] on prolonged contact with silica gel.

***t*-2-Bromo-*t*-3-*tert*-butyl-*r*-1-cyclohexanol Acetate (4d).** Prepared from **4c** with Ac_2O in pyridine for 14 h at room temperature as a liquid: NMR δ 0.96 [s, $-C(CH_3)_3$, 9 H], 2.01 (s, CH_3CO–, 3 H), 4.35 (m, $W_{1/2}$ = 6.5 Hz, >CHBr, 1 H), 4.97 (m, $W_{1/2}$ = 6.5 Hz, >CHO-$COCH_3$, 1 H).

Anal. Calcd for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.63; Br, 28.83. Found: C, 52.40; H, 7.62; Br, 28.35.

***t*-2-Bromo-*t*-6-*tert*-butyl-*r*-1-cyclohexanol acetate (5d),** obtained from **5c** and Ac_2O in pyridine after 21 days, had mp 32–34 °C (from petroleum ether): NMR δ 0.90 [s, $-C(CH_3)_3$, 9 H], 2.04 (s, CH_3CO–, 3 H), 3.85 (m, W = 25 Hz, >CHBr, 1 H), 4.92 (t, J = 9.6 Hz, >CHOCOCH$_3$, 1 H).

Anal. Calcd for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.63; Br, 28.83. Found: C, 52.20; H, 7.35; Br, 28.40.

***t*-2-Bromo-*c*-6-*tert*-butyl-*r*-1-cyclohexanol acetate (6d)** was obtained as a liquid from **6c** and Ac_2O after a reaction time of 160 h: NMR δ 0.88 [s, $-C(CH_3)_3$, 9 H], 2.04 (s, CH_3CO–, 3 H), 4.31 (m, $W_{1/2}$ = 6.5 Hz, >CHBr, 1 H), 5.17 (m, $W_{1/2}$ = 6.5 Hz, >CHOCOCH$_3$, 1 H).

Anal. Calcd for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.63; Br, 28.83. Found: C, 52.41; H, 7.60; Br, 28.55.

***t*-2-Bromo-*c*-3-*tert*-butyl-*r*-1-cyclohexanol Acetate (7d).** A mixture of acetoxy bromides **4d–7d** (4.5 g), obtained by the addition of acetyl hypobromite to **1a** as described above, was chromatographed on a 2.8 × 70 cm column of silica gel (140 g). Petroleum ether eluted in succession mixtures of **4d** and **6d** (0.6 g), mixtures of **4d, 6d,** and **7d** (0.6 g), and pure **7d** (2.5 g): mp 55 °C (from petroleum ether); NMR δ 1.08 [s, $-C(CH_3)_3$, 9 H], 2.02 (s, CH_3CO–, 3 H), 3.88 (t, J = 8.8 Hz, >CHBr, 1 H), 4.90 (m, W = 23 Hz, >CHOCOCH$_3$, 1 H).

Anal. Calcd for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.63; Br, 28.83. Found: C, 52.05; H, 7.58; Br, 29.10.

***trans*-3-*tert*-Butyl-1,2-epoxycyclohexane (2a).** Bromohydrin **5c** (1.0 g, 4.2 mmol) was dissolved in 2-propanol (20 mL) and titrated with 1 N aqueous NaOH at room temperature, with phenol phthalein as the indicator. The consumption of base amounted to 4.2 mL. Dilution with water, extraction with ether, and usual workup gave pure (GLC) **2a**[6] (0.6 g), bp 92–94 °C (20 mm).

The same epoxide was also obtained by similar treatment of **4c.**

***cis*-3-*tert*-Butyl-1,2-epoxycyclohexane (3a). A.** Cyclization of bromohydrin **6c** (1.0 g) under the same conditions as employed for **4c** and **5c** afforded pure (GLC) **3a**[6] (0.55 g), bp 82–83 °C (18 mm).

B. A solution of K_2CO_3 (2.0 g) in water (5 mL) was added to **7d** (2.0 g) dissolved in CH_3OH (50 mL). After refluxing for 2 h, dilution with water, extraction with ether, and usual workup gave 0.8 g of pure **3a.**

***cis*-3-Methyl-1,2-epoxycyclohexane (3b).** The procedure of Rickborn[14] was modified as follows: a 0.36 M $CHCl_3$ solution of peroxybenzoic acid (300 mL) was added dropwise to **1b** (8.5 g, 0.088 mol) dissolved in $CHCl_3$ (25 mL) at 0 °C. After 12 h the solution was washed with saturated aqueous Na_2CO_3 and water, dried, and evaporated to give a mixture of **2b** and **3b** (8.0 g) in a ratio of 52:48 (GLC: 50-m capillary column coated with polypropylene glycol; column 90 °C, evaporator and detector 140 °C, nitrogen flow 1 mL/min; relative retention times 1.10:1). A solution of this mixture in $CHCl_3$ (25 mL) was saturated with dry HCl at 0 °C. After 5 min, usual workup yielded a residue (9.0 g) consisting of chlorohydrins **4i–7i,** which was dissolved in anhydrous pyridine (100 mL) and treated with *p*-nitrobenzoyl chloride (11.5 g). After 10 h at room temperature the reaction mixture was poured onto 10% aqueous HCl and ice and extracted with petroleum ether. Usual workup gave a solid which was crystallized from CH_3OH. Six crystallizations yielded 3.0 g of the pure *p*-nitrobenzoate **6j,** mp 112–113 °C (lit.[14] mp 109–110 °C).

A solution of **6j** (3.0 g) in CH_3OH (45 mL) and water (5 mL) was refluxed for 1 h in the presence of K_2CO_3 (3.5 g). Dilution with water, extraction with ether, and distillation of the dried extract afforded pure (GLC) **3b**[14] (0.8 g), bp 48 °C (18 mm).

***trans*-3-Methyl-1,2-epoxycyclohexane (2b).** NBS (9.5 g, 0.053 mol) was added portionwise to a stirred solution of **1b** (5.0 g, 0.052 mol) in Me_2SO–water (95:5, 100 mL) at room temperature. The reaction mixture was stirred for 30 min, diluted with water, and extracted with ether. Usual workup gave 9.3 g of mixed bromohydrins **4g–7g,** which were dissolved in anhydrous pyridine and esterified with *p*-nitrobenzoyl chloride (9.5 g) in the usual way. Crystallization of the resulting *p*-nitrobenzoates from ethanol yielded pure **4h** (9.5 g), mp 118–119 °C.

Anal. Calcd for $C_{14}H_{16}BrNO_4$: C, 49.14; H, 4.71. Found: C, 49.14; H, 4.86.

Hydrolysis of **4h** (9.5 g) with K_2CO_3 in aqueous CH_3OH as described for **6j** afforded 2.5 g of pure (GLC) **2a,** bp 48–49 °C (18 mm).

***t*-2-Bromo-*t*-3-methyl-*r*-1-cyclohexanol (4g).** A mixture of **4g–7g** (3.0 g) obtained by reaction of **1b** with NBS in Me_2SO–water as described above was chromatographed on a 1.8 × 50 cm column of silica gel (70 g). Elution with petroleum ether–ethyl ether (96:4) yielded small amounts of mixtures and finally pure **4g,** as a liquid: NMR δ 1.03 (d, J = 6.5 Hz, $-CH_3$, 3 H), 3.52 (s, –OH, 1 H), ~4.05 (two overlapping m, >CHOH and >CHBr, 2 H).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.53; H, 6.76. Found: C, 43.80; H, 6.90. *p*-Nitrobenzoate (**4h**), mp 118–119 °C.

***t*-2-Bromo-*t*-6-methyl-*r*-1-cyclohexanol (5g).** A solution of **2b** (3.0 g) in $CHCl_3$ (75 mL) was saturated with dry HBr. After 15 min, washing with water, 10% aqueous $NaHCO_3$, and water, drying and evaporation gave 4.0 g of a mixture of **4g** and **5g,** which was chromatographed on a 1.8 × 60 cm column of silica gel (75 g). Elution with 96:4 petroleum ether–ethyl ether gave pure **5g** (1.0 g), mp 36–37.5 °C (from petroleum ether); NMR δ 1.08 (highly distorted d, $-CH_3$, 3 H), 2.68 (s, –OH, 1 H), 3.23 (t, J = 8.4 Hz, >CHOH, 1 H), 3.96 (m, W = 25 Hz, >CHBr, 1 H).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.54; H, 6.76; Br, 41.38. Found: C, 43.73; H, 6.84; Br, 41.10.

p-Nitrobenzoate (**5h**): mp 136–138 °C

Anal. Calcd for $C_{14}H_{16}BrNO_4$: C, 49.14; H, 4.71. Found: C, 49.00; H, 4.85.

Further elution with 95:5 petroleum ether–ethyl ether yielded pure **4g** (2.3 g).

***t*-2-Bromo-*c*-6-methyl-*r*-1-cyclohexanol *p*-Nitrobenzoate (6h).** Opening of **3b** (0.4 g) with dry HBr in $CHCl_3$ followed by esterification of the crude oily product with *p*-nitrobenzoyl chloride in pyridine and crystallization from CH_3OH yielded **6h** (0.5 g), mp 128–130 °C.

Anal. Calcd for $C_{14}H_{16}BrNO_4$: C, 49.14; H, 4.71. Found: C, 49.10; H, 4.90.

***t*-2-Bromo-*c*-3-methyl-*r*-1-cyclohexanol *p*-Nitrobenzoate (7h).** A 1 M aqueous solution of HOBr[34] (35 mL) was added dropwise with stirring to **1b** (3.0 g, 0.032 mol) dissolved in dioxane (100 mL). After 30 min at room temperature, dilution with water, extraction with ether, and the usual workup yielded 4.2 g of mixed bromohydrins **4g–7g,** which were chromatographed on a 1.8 × 60 cm column of silica gel. Elution with 97:3, 95:5, and 90:10 petroleum ether–ethyl ether gave various mixtures of **6g** and **7g,** and finally **4g.**

A sample (0.2 g) of an approximate 1:1 mixture of **6g** and **7g** was esterified with *p*-nitrobenzoyl chloride (0.24 g) in anhydrous pyridine (2 mL). The resulting mixed *p*-nitrobenzoates **6h** and **7h** (0.26 g) were subjected to preparative TLC (PSC-Fertigplatten Kieselgel 60 F_{254} Merck). Elution was repeated three times with 97:3 and once with 96:4 petroleum ether–ethyl ether. Extraction of the slower moving band with ethyl ether and purification of the product by further TLC and crystallization from CH_3OH yielded pure **7h** (50 mg), mp 103–104 °C.

Anal. Calcd for $C_{14}H_{16}BrNO_4$: C, 49.14; H, 4.71. Found: C, 48.91; H, 4.95.

Extraction of the faster moving band and crystallization from CH_3OH gave pure **6h** (50 mg).

3-Methyl-2-cyclohexenone 2,4-Dinitrophenylhydrazone (9). A solution of **4g** (0.72 g, 3.7 mmol) in acetone (10 mL) was treated at 0 °C with Jones reagent[36] (1 mL). After 3 h, dilution with water, extraction with ether and usual workup gave bromo ketone 8 (0.65 g) as a liquid: NMR δ 1.08 (d, J = 6 Hz, $-CH_3$, 3 H), 4.20 (m, $W_{1/2}$ = 5 Hz, >CHBr, 1 H). This product was dissolved in warm glacial acetic acid (10 mL), 2,4-dinitrophenylhydrazine (0.70 g) was added under a nitrogen atmosphere, and the solution was heated on a hot plate for 5 min. The hydrazone **9,** precipitated immediately and crystallized several times from chloroform–ethanol, had mp 175–178 °C (lit.[16] mp 177–178 °C).

***t*-2-Chloro-*t*-3-methyl-*r*-1-cyclohexanol (4i) and *t*-2-chloro-*t*-6-methyl-*r*-1-cyclohexanol (5i).** A solution of **2b** (1.0 g) in $CHCl_3$ (50 mL) was saturated with dry HCl. After 15 min, usual workup gave a mixture of **4c** and **5c** (1.2 g) which was chromatographed on a 1.8 × 50 cm column of silica gel. Elution with 96:4 petroleum ether–ethyl ether gave pure **5i** (0.1 g) as a low-melting solid; *p*-nitrobenzoate (**5j**): mp 124–126.5 °C (from CH_3OH).

Anal. Calcd for $C_{14}H_{16}ClNO_4$: C, 56.50; H, 5.40. Found: C, 56.80; H, 5.40.

Further elution with 95:5 petroleum ether–ethyl ether yielded pure **4i** (0.4 g), liquid: *p*-nitrobenzoate (**4j**) mp 98–99 °C (from CH_3OH).

Anal. Calcd for $C_{14}H_{16}ClNO_4$: C, 56.50; H, 5.40. Found: C, 56.75; H, 5.25.

***t*-2-Chloro-*c*-6-methyl-*r*-1-cyclohexanol (6i) and *t*-2-Chloro-*c*-3-methyl-*r*-1-cyclohexanol (7i).** NCS (7.5 g, 0.056 mol) was added to a stirred suspension of **1b** (5.0 g, 0.052 mol) in water (35 mL) heated at 90 °C in a flask equipped with a condenser. Heating was continued until a heavy oil was formed. Extraction with ether, usual workup, and distillation gave a mixture of chlorohydrins **4i–7i** (5.5 g), bp 62–65 °C (2.5 mm), which was chromatographed on a 1.8 × 70 cm column of silica gel. Elution with 98:2 petroleum ether–ethyl ether gave in succession: **5i,** as a low-melting solid; **6i,** as a liquid; mixtures of **6i** and **7i;** mixtures of **7i** and **4i.** Further elution with 95:5 petroleum ether–ethyl ether yielded pure **4i.**

Esterification of **6i** with *p*-nitrobenzoyl chloride gave **6j,** mp 112–113 °C, identical to the *p*-nitrobenzoate used for the preparation of epoxide **3b.** The same compound was also obtained by esterification of the product of ring opening of **3b** with HCl in $CHCl_3$ and crystallization from CH_3OH.

Treatment of a mixture of **6i** and **7i** with *p*-nitrobenzoyl chloride followed by several crystallizations from CH_3OH afforded ester **7j** contaminated by ~20% (NMR) of isomer **6j.**

Anal. Calcd for $C_{14}H_{16}ClNO_4$: C, 56.50; H, 5.40. Found: C, 57.00; H, 5.70.

Products Distribution Studies. Additions to Alkenes. The additions reported in Tables I and IV were performed under the same conditions employed for the preparative reactions described above. The reaction of **1a** with NCS in water was carried out as described for **1b.** The additions of NBS–water to both **1a** and **1b** were performed in the following way: the olefin (10 mmol) was added dropwise to a stirred suspension of NBS (2.5 g, 14 mmol) in water (25 mL). The mixture was stirred for 2 h at room temperature and extracted with ether. The extract was washed with water, dried, and evaporated.

All reactions were carried out on a 10-mmol scale and the crude products were subjected to GLC under the following conditions.

Bromohydrins **4c–7c:** 1.5-m glass column, 2.5-mm i.d., packed with 10% ethylene glycol succinate on silanized Chromosorb W 80–100 mesh (column 115 °C, evaporator and detector 200 °C, nitrogen flow 35 mL/min). Relative retention times: **5c,** 1; **7c,** 1.49; **6c,** 2.43; **4c,** 3.22.

Acetoxy bromides **4d–7d:** 1.5-m glass column, 2.5-mm i.d., packed with 1% silicone oil SE_{52} on silanized Chromosorb W 80–100 mesh (column 60 °C, evaporator and detector 150 °C, nitrogen flow 40 mL/min). Relative retention times: **6d,** 1; **4d,** 1.11; **5d** and **7d,** 1.55. Since under these conditions the diequatorial adducts **5d** and **7d** were not separated, only the single percentages of **4d** and **6d** and the total percentage of **5d** and **7d** were obtained. The single percentages of the latter adducts were deduced by combining the data obtained by direct analysis of the mixture of acetoxy bromo adducts with the percentages of epoxides **2a** and **3a** arising from K_2CO_3 hydrolysis of the same mixture.

Chlorohydrins **4f–7f** and **4i–7i** and bromohydrins **4g–7g:** 2-m glass column, 2.5-mm i.d., packed with 10% Carbowax 20 M on silanized Chromosorb W 80–100 mesh. Relative retention times of **4f–7f** (column 170 °C, evaporator and detector 220 °C, nitrogen flow 30 mL/min): **5f,** 1; **7f,** 1.42; **6f,** 2.33; **4f,** 2.96. Relative retention times of **4g–7g** (column 160 °C, evaporator and detector 200 °C, nitrogen flow 30 mL/min): **5g,** 1; **7g,** 1.16; **6g,** 2.28; **4g,** 3.21. Relative retention times of **4i–7i** (column 150 °C, evaporator and detector 200 °C, nitrogen flow 30 mL/min): **5i,** 1; **7i,** 1.17; **6i,** 2.16; **4i,** 2.92.

All products were stable under the reaction conditions and under the GLC conditions. The percentages quoted in Tables I and V for each reaction are averages of at least four experiments, which were reproducible within ±1%.

Opening of Epoxides with Hydrogen Halides. A solution of epoxide **2a, 2b, 3a,** and **3b** (0.1 g) in 5 mL of solvent was saturated with the appropriate dry hydrogen halide. After 15 min at room temper-

ature, the reaction mixture was washed with water and 10% aqueous $NaHCO_3$, dried, and subjected to GLC under the conditions defined above. The results reported in Tables II and IV are averages of three or more experiments, which were reproducible within ±1%.

Acknowledgments. This work has been supported in part by a grant from the Consiglio Nazionale della Ricerche.

Registry No.—**1a,** 14072-87-8; **1b,** 591-48-0; **2a,** 20887-61-0; **2b,** 7443-54-1; **3a,** 20887-60-9; **3b,** 7443-69-8; **4c,** 64199-99-1; **4d,** 64200-00-6; **4g,** 64200-01-7; **4i,** 64162-78-3; **5c,** 38512-63-9; **5c** phenylurethane, 38749-39-2; **5d,** 38512-66-2; **5g,** 64162-79-4; **5i,** 64162-80-7; **6c,** 38512-64-0; **6d,** 64199-91-3; **6g,** 64199-92-4; **6i,** 64199-93-5; **7c,** 38749-36-9; **7d,** 38512-65-1; **7e,** 38749-37-0; **7g,** 64162-81-8; **7i,** 64199-94-6; **8,** 41780-49-8; **9,** 3234-76-2; *p*-nitrobenzoyl chloride, 122-04-3.

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(19) Evidence has been presented that Me_2SO can be the actual nucleophile in the reaction of olefins with NBS in a mixture of Me_2SO and water (see ref 11).
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Epoxycarbinyl Solvolyses. Lack of Significant Participation by Epoxide Oxygen in the Hydrolysis of Acyclic Secondary Epoxycarbinyl Substrates

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Received May 26, 1977

The rate constants and activation parameters for solvolysis of the diastereomeric epoxycarbinyl *p*-bromobenzenesulfonate esters **23b** and **24b** (derived from the oxides of *trans*-3-penten-2-ol) in ethanol–water mixtures have been determined. The predominant products (~88–96%) from solvolysis of **23b** and **24b** in 80% acetone–water resulted from inversion at the ionizing carbon. The product distributions suggest that neither significant amounts of oxabicyclobutonium ion intermediates nor highly stabilized epoxycarbinyl cations are formed. The rates of solvolysis of **23b** and **24b** were ~10^6 times slower than the rates of solvolysis of the corresponding cyclopropylcarbinyl analogues.

Numerous publications about the solvolytic reactions of cyclopropylcarbinyl substrates have appeared during the past 20 years.[1] The stabilizing interaction of the cyclopropane ring with a developing positive charge on the carbinyl carbon is generally reflected by enhanced reactivities of cyclopropylcarbinyl derivatives, relative to model compounds without neighboring cyclopropyl groups. The geometry of the cyclopropyl group relative to the developing p orbital on the carbinyl carbon is critical, however. A "bisecting" geometry of the cyclopropyl group is most favorable, whereas a "perpendicular" geometry actually brings about a destabilizing interaction.[1,2]

More recent results have been reported on the reactions of geometrically related "epoxycarbinyl" substrates of general structure **1** under conditions that lead to the development of a positive charge on the carbinyl carbon.[3-5] Most of the reactions of epoxycarbinyl substrates are analogous to those reactions observed in cyclopropylcarbinyl solvolysis. If the intermediate from the solvolysis of **1** possesses a significant positive charge density on the carbinyl carbon (i.e., **2**), then

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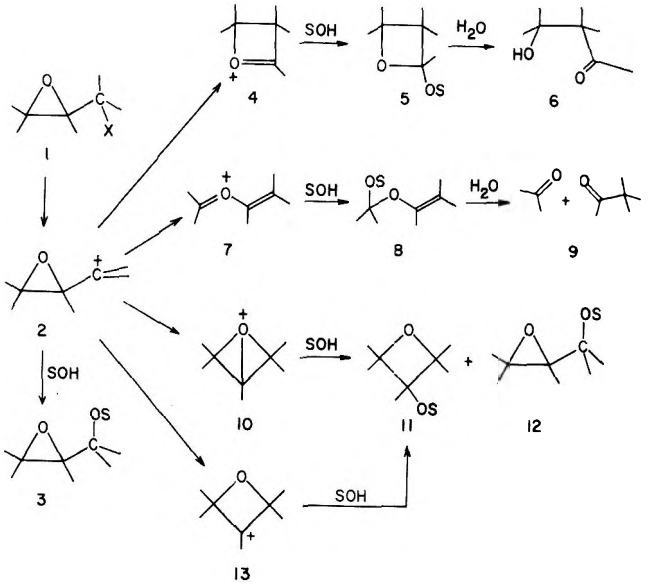
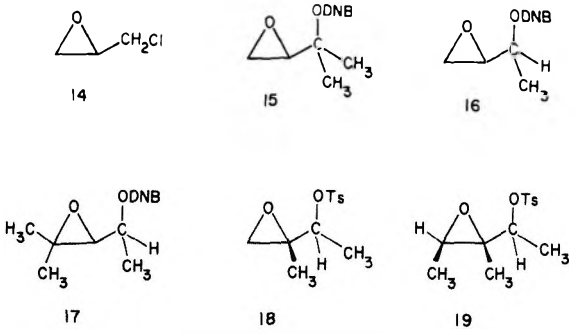
Scheme I



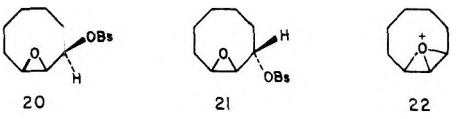
product **3** retaining the epoxycarbinyl structure would be anticipated. However, the epoxycarbinyl derivative **1** can also potentially rearrange in either concerted pathways or via **2** to other intermediates **4, 7, 10,** or **13**. Migration of the carbon–carbon bond or the carbon–oxygen bond of the epoxide group in **2** to the electron-deficient center would yield oxonium ion **4** or 3-oxetanyl cation **13**, respectively, and would be analogous to the cyclopropylcarbinyl–cyclobutyl cation rearrangement. Intermediate **4**, in water, would eventually yield β-ketols. In a reaction related to the cyclopropylcarbinyl–homoallyl interconversion, rupture of the carbon–carbon bond of the epoxide group in **2** yields oxonium ion **7**, the precursor to carbonyl products **9**. There is also the possibility that the nonbonding electrons on the oxygen in **2** would interact with the adjacent positive charge on the carbinyl carbon, thereby leading to an intermediate oxabicyclobutonium ion **10**. Intermediate **10** can potentially yield products **11** and **12**.

The solvolytic reactions of epichlorohydrin (**14**) and 3,5-dinitrobenzoate esters **15–17** have been reported to yield 3-



oxetanyl products, and oxabicyclobutonium ions were suggested as possible intermediates.[3] The study of the solvolysis of epichlorohydrin (**14**) was hindered, however, because any solvolysis products that retained the epoxycarbinyl structure could not have survived the reaction conditions.[3a] The *erythro*- and *threo*-*p*-toluenesulfonate esters **18** and **19** hydrolyzed to yield predominantly β-ketols (>80%), presumably via a 2-oxetanyl cation **4**.[5a] Anchimeric assistance by the neighboring epoxide was invoked to explain the hydrolysis product distributions.

Oxabicyclobutionium ion **22** was ruled out as an intermediate in the hydrolysis of the epimeric medium-ring epoxycarbinyl brosylates **20** and **21**,[4] although geometric constraints of the medium ring may have made such intermediate unlikely. Rearrangement products from intermediate oxonium



ions of the structural types **4** and **7** were observed, however, in addition to products that retained the epoxycarbinyl structure. It was estimated that epimeric esters **20** and **21** were both about 6–7 powers of ten less reactive than their cyclopropylcarbinyl analogues. Likewise, it can be estimated from published rate data[5a] that **18** and **19** are considerably less reactive toward hydrolysis than related cyclopropylcarbinyl systems.[6] Therefore, the epoxide group appears much less effective than cyclopropyl for stabilizing a developing positive charge on the carbinyl carbon. These reactivities seem to be inconsistent with one set of calculations that suggest that the carbon–carbon bond of an epoxide group should stabilize the positive charge on the adjacent carbinyl carbon as effectively as carbon–carbon bonds of cyclopropanes do for certain geometries.[7]

In view of the fact that medium-ring constraints in the solvolysis of **20** and **21** may have made the formation of **22** unlikely and since oxabicyclobutonium ions had already been postulated as intermediates in the solvolysis of several simple epoxycarbinyl systems,[3] we have undertaken a study of the hydrolysis of the epimeric epoxycarbinyl brosylates **23b** and **24b**, in which the carbinyl carbon is secondary. Esters **23b** and **24b** are free of any medium-ring constraints for formation of

23a, R = H
b, R = Bs

24a, R = H
b, R = Bs

oxabicyclobutonium ion intermediates, and maximum stabilization of the developing positive charge by the epoxide ring can be attained by rotation about the C_2–C_3 bond for the preferred geometry. Compounds **23b** and **24b** also do not possess a β-methyl group such as *p*-toluenesulfonate esters **18** and **19**. The β-methyl groups of **18** and **19** give rise to neopentyl-type structures which result in appreciable steric hindrance to solvation at the carbinyl carbon and are prone to rearrangement.[8]

Results

Epoxidation of *trans*-3-penten-2-ol with *m*-chloroperbenzoic acid yielded a mixture of diastereomeric epoxycarbinols **23a** and **24a** in a 65:35 ratio. The relative stereochemistry of the hydroxyl group relative to the oxirane ring for either of the products was not established. For purposes of discussion, the structure **23a** was assigned to the major component of the product mixture, and, consequently, the structure **24a** was assigned to the minor component. The products were separated by preparative gas chromatography and converted to their *p*-bromobenzenesulfonate esters. The rates for solvolysis of **23b** and **24b** were determined ethanol–water mixtures at several temperatures and are listed in Table I. The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for solvolysis of **23b** and **24b** in 80% ethanol–water are also provided.

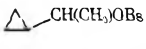
Isomer **23b** hydrolyzed in 90% acetone–water to yield a mixture of epoxycarbinols containing ~96% of inverted product **24a**, and ~4% of retained alcohol **23a**. No products with gas chromatography retention times different from **23a** and **24a** could be detected. Brosylate **24b** hydrolyzed under the same conditions to yield 88% of inverted product **23a** and ~12% of retained product **24a**. As in the hydrolysis of **23b**, no other products from **24b** could be detected by gas chromatographic analysis of the product mixture.

Table I. First-Order Rate Constants[a] and Activation Parameters[a] for Solvolysis of 23b and 24b in Ethanol–Water Mixtures[b]

Compd	Registry no.	Temp, °C	$10^5 k$, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, kcal/mol
			80% Ethanol–Water		
23b	64312-47-6	75.00	64.8 ± 0.4		
		70.10	41.3 ± 0.6		
		64.83	26.0 ± 0.8		
		59.75	15.4 ± 0.2		
		35.2	1.34 ± 0.01		
		25.0	0.36[c]	20.8 ± 0.2	−13.6 ± 0.6
24b	64252-18-2	69.95	26.6 ± 0.7		
		64.95	16.4 ± 0.8		
		59.85	11.0 ± 0.4		
		35.2	0.99 ± 0.07[d]		
		25.0	0.29[c]	19.7 ± 0.6	−17.6 ± 1.9
			60% Ethanol–Water		
23b		35.2	2.48 ± 0.02		
24b		35.2	2.24 ± 0.01		
			50% Ethanol–Water		
23b		35.2	3.50 ± 0.01		
24b		35.2	3.76 ± 0.02[d]		

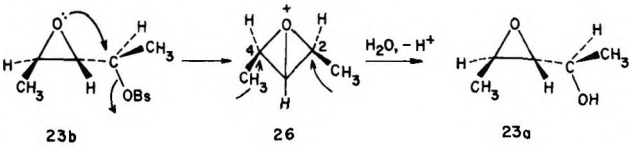
[a] Calculated by nonlinear regression analysis. Errors are given in units of standard deviation. [b] v/v. The percent listed corresponds to the percent of ethanol. Triethylamine was added as a buffering reagent. [c] Extrapolated from rates at higher temperatures. [d] Average of two kinetic runs.

Table II. Relative Rates of Solvolysis of Several Brosylate Esters in 80% Ethanol–Water at 25 °C

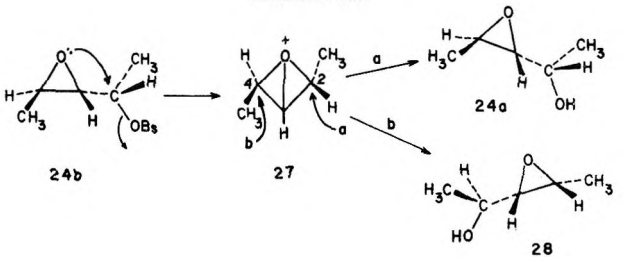
Compound	k_{rel}, s^{-1}
Isopropyl brosylate[a]	0.8
sec-Butyl brosylate[b]	1.0
23b	0.19
24b	0.15
 (25)[c]	~10^6

[a] Reference 14. [b] V. J. Shiner, Jr., "Isotope Effects in Chemical Reactions", C. J. Collins and N. S. Bowman, Ed., *Van Nostrand-Reinhold, New York, N.Y., 1970*, p 129. [c] Reference 6. Rates were extrapolated to common solvent, temperature, and leaving group.

Scheme II



Scheme III

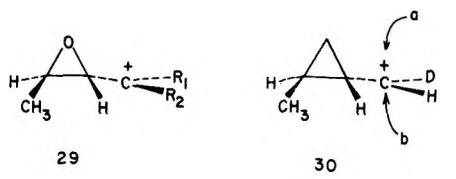


Discussion

The *relative rates of solvolysis of* **23b**, **24b**, *and several other* model compounds are listed in Table II. If an epoxide group were able to stabilize the development of a positive charge on an adjacent carbon as efficiently as a cyclopropane ring, then the relative rates of solvolysis of **23b**, **24b**, and α-methylcyclopropylcarbinyl brosylate (**25**) would be expected to be similar. As Table II indicates, however, **23b** and **24b** are about 10^6 times less reactive to solvolysis than the geometrically related cyclopropylcarbinyl analogue. Therefore, in these simple secondary acyclic epoxycarbinyl derivatives and in several medium-ring epoxycarbinyl derivatives,[4] the epoxide groups are not nearly as effective as cyclopropyl groups in stabilizing an adjacent positive charge on carbon. In fact, **23b** *and* **24b** *are ca. five times less reactive than sec-butyl* brosylate, an ester of similar structure to **23b** and **24b** except that the epoxide moieties of **23b** and **24b** have been replaced by ethyl groups. Because of the different structures of **23b** and **24b** compared to *sec*-butyl brosylate, the small differences of solvolytic reactivities might be attributed to either a destabilizing electronic effect of an epoxide group or to different steric requirements of an epoxide moiety relative to an ethyl group.

Because of the lack of a suitable model for estimating the rates of solvolysis of **23b** and **24b** in the absence of participation by the epoxide group, knowledge of the product compositions is essential to understanding the mechanisms of their solvolytic reactions. If **23b** were to solvolyze with participation of the *n* electrons of the adjacent epoxide group, an intermediate oxabicyclobutonium ion **26** would form (Scheme II). Because of its symmetrical structure, **26** should collapse with solvent at either C_2 or C_4 with inversion to yield a single product **23a**, an overall process that would give rise to retention of stereochemistry.[9] Ionization of the diastereomeric alcohol **24b** with participation of the *n* electrons of oxygen, however, would result in the formation of oxabicyclobutonium ion **27** (*Scheme II*). Intermediate **27**, however, does not possess a plane of symmetry. Whereas collapse of solvent at C_2 of **27** would yield **24a**, a process involving overall retention of stereochemistry, collapse of solvent at C_4 of **27** would yield **28**, an epoxycarbinol derived from *cis*-3-penten-2-ol.[9]

If participation by the *n* electrons of oxygen in the solvolysis of **23b** and **24b** did not occur, but rather an intermediate **29** were formed in which charge is located primarily at C_2, then solvolysis of **23b** and **24b** should yield mixtures of only **23a** and **24a**. The stabilized cyclopropylcarbinyl cation **30** yields 72% of product from collapse of water at the top side (a) and 28%



29 30

of product from collapse of water at the bottom side (b).[10] A stabilized cation **29** might therefore be expected to give similar results, i.e., significant collapse of solvent from both sides of the cationic center.

The actual product distributions observed in the solvolysis of **23b** and **24b**, resulting from predominant inversion at C_2, suggest that neither significant amounts of oxabicyclobutonium ions **26** and **27**, nor a highly stabilized cation **29** are formed. The results of solvolysis of **23b** and **24b** are very similar to those observed in the solvolysis of simple secondary systems such as 2-butyl or 2-octyl *p*-bromobenzenesulfonates, namely, predominant inversion at the ionizing center.[11] Such inversion is observed in acyclic systems when the intermediate is an unstabilized primary[12] or secondary cation, and results from either an S_N2-type displacement by a solvent molecule or collapse of an intermediate tight ion pair with a solvent molecule preferentially at the backside of the ionizing carbon.

The Grunwald–Winstein *m* values[13] for solvolyses of **23b** and **24b** in ethanol–water solutions (Table I) were calculated to be 0.20 and 0.34, respectively. In the absence of anchimeric assistance, low *m* values generally reflect a high degree of solvent participation at the transition state. For instance, *m* values for isopropyl brosylate and *sec*-butyl tosylate are 0.44[14] and 0.47,[15] respectively. Both low *m* values and predominant inversion at ionizing carbon are consistent with high degrees of solvent involvement of a nucleophilic nature at the transition states for solvolysis of **23b** and **24b** in ethanol–water mixtures. These results do not preclude the possibility that in more highly-ionizing, less nucleophilic solvents **23b** and **24b** may solvolyze by different mechanisms.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer, and ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-20A spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Preparation of 23a and 24a. To a solution of 4.9 g (0.057 mol) of *trans*-3-penten-2-ol[16] in 100 mL of methylene chloride stirred in an ice–water bath was added 13.0 g of *m*-chloroperbenzoic acid[16] over a period of 5 min. The reaction mixture was stirred at 0 °C for an additional hour, and the solid precipitate of *m*-chlorobenzoic acid was separated by suction filtration and washed with cold methylene chloride. The filtrate was washed with saturated sodium bicarbonate solution (2 × 75 mL), and the solvent was removed at aspirator pressure. The residue was distilled in a short-path distillation apparatus under reduced pressure (15 mm) at a bath temperature of 85 °C to yield 4.1 g (70%) of a clear oil that consisted of 65% **23a** and 35% **24a**:[17] IR (CCl_4) 3600–3100 cm^{-1}.

The products were separated by preparative gas chromatography on a 12 ft × ¼ in. 20% diethylene glycol succinate (DEGS) column at 80 °C: retention time of **23a** 26.5 min; retention time of **24a** 24.0 min.

The NMR spectrum (CCl_4) of **23a** consisted of absorptions at δ 1.1–1.3 (6 H, CH_3), 2.44 (d of d, 1 H, C_3 H), 2.77 (m, 1 H, C_4 H), 3.38 (m, 1 H, CHOH), and the NMR spectrum (CCl_4) of **24a** possessed absorptions at δ 1.1–1.3 (6 H, CH_3), 2.45 (ca. t, 1 H, C_3H), 2.82 (m, 1 H, C_4H), and 3.65 (m, 1 H, CHOH).

Anal. (**24a**) Calcd for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.65; H, 10.05.

***p*-Bromobenzenesulfonate Ester 23b.** Powdered potassium hydroxide (4.0 g of 85% KOH, 71 mmol) was added to a solution of 142 mg (1.39 mmol) of **23a** (contaminated with 5% of **24a**) and 402 mg (1.57 mmol) of *p*-bromobenzenesulfonyl chloride in 6 mL of diethyl ether. The resulting suspension was stirred in an ice–water bath for 1 h. An additional 20 mL of diethyl ether was added, and the reaction mixture was dried with anhydrous calcium sulfate and filtered. Removal of the solvent yielded 348 mg (ca. 78%) of **23b**, which was recrystallized from a diethyl ether–pentane solution to yield 271 mg of **23b**: mp 37.5–38.5 °C; NMR (CCl_4) δ 1.1–1.4 (6 H, methyl absorptions), 2.45–2.85 (m, 2 H, protons on epoxide ring), 4.23 (pentet, 1 H, J = 6 Hz, CHOBs), 7.43 (s, 4 H, aromatic protons).

Anal. Calcd for $C_{11}H_{13}O_4SBr$: C, 41.14; H, 4.08. Found: C, 41.04; H, 4.17.

***p*-Bromobenzenesulfonate ester 24b** was prepared from 30 mg of **24a** (containing ~4% of **23a**) by the same procedure outlined above for the preparation of **23b**. The product was further dried under vacuum (2 mm): yield 74 mg (~78%) of clear oil; NMR (CCl_4) δ 1.1–1.4 (6 H, methyl absorptions), 2.40–2.75 (m, 2 H, protons on epoxide ring), 4.14 (pentet, 1 H, J = 6 Hz, CHOBs), 7.43 (s, 4 H, aromatic protons).

Anal. Calcd for $C_{11}H_{13}O_4SBr$: C, 41.14; H, 4.08. Found: C, 41.07; H, 4.21.

Kinetic Procedures. A. Approximately 15 mg of **23b** or **24b** and 15 μL of triethylamine were dissolved in 25 mL of an ethanol–water solution. Approximately 2.5 mL of this solution was sealed in each of ten ampules. The ampules were then placed in a constant-temperature oil bath, thermostated to within ±0.03 °C of the stated temperatures (Table I). At a given time, an ampule was removed, and the absorbance of the solution was measured at 265 nm in a Gilford 2400 spectrophotometer.[18]

B. The rates of solvolyses of **23b** and **24b** at 35.2 °C were determined by monitoring the absorbance of the reaction solution at 265 nm in the thermostated cell compartment of a Gilford 2400 spectrophotometer.

Rate constants were obtained by nonlinear regression analysis of the data, for each kinetic run, by a Wang 700 calculator computer.

Product Analyses. A solution of ca. 30 mg of **23b** or **24b**, 1.2 mL of 90% acetone–water (v/v), and 30 μL of triethylamine was sealed in an ampule and placed in an oil bath for 20 h (ca. 10 half-lines). The reaction solution was diluted with ca. 10 mL of water and continuously extracted with diethyl ether for 6 h. Most of the organic solvent was distilled through a 10-cm column packed with glass helices, and the residual solution was analyzed by gas chromatography on a 10% diethylene glycol succinate column (15 ft × ⅛ in.) at 90 °C. Cyclopentanol (7.0 mg) was added to the product mixture to serve as an internal standard for chromatographic analysis. The yields from the hydrolysis of **23b** and **24b** were generally 85–95%.

The products from the hydrolysis of **23b** were **24a** (~96%) and **23a** (~4%). The major product was separated by preparative GLC and identified as **24a** by its infrared spectrum. The minor product possessed the same GLC retention time as **24a**.

The products from the hydrolysis of **24b** (estimated to contain ~4% of **23b**) were ~84% of **23a** and ~16% of **24a**. Both products were separated by preparative GLC and identified by infrared spectroscopy. Since it was estimated that **24b** was contaminated with ~4% of **23b**, the product composition was corrected for the fact that **23b** undergoes predominant inversion when hydrolyzed. Therefore, we estimate that pure **24b** yields ~88% of **23a** and ~12% of **24a**.

Acknowledgment. This research was supported by a Frederick Gardner Cottrell Grant administered by the Research Corporation.

Registry No.—**23a**, 26091-69-0; **24a**, 22520-29-2; *trans*-3-penten-2-ol, 3899-34-1; *p*-bromobenzenesulfonyl chloride, 98,58,8.

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Epoxycarbinyl Solvolyses. The Solvolytic Reactions of *syn*- and/*anti*-9-Oxabicyclo[6.1.0]non-2-yl *p*-Bromobenzenesulfonates

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Received May 26, 1977

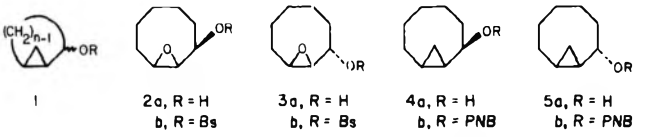
The rates of solvolysis of *syn*- and *anti*-9-oxabicyclo[6.1.0]non-2-yl *p*-bromobenzenesulfonates (**2b** and **3b**) have been determined and were found to be ~10^7 times slower than those of the corresponding cyclopropylcarbinyl analogues **4b** and **5b**. The product distributions from hydrolysis of **2b** and **3b** have been found to be quite complex and consisted of 50–60% of rearranged products, in addition to elimination and unrearranged products. *anti*-Brosylate **2b** yielded 29% of product that resulted from a transannular 6,2 hydride shift, followed by stereospecific collapse of solvent with the rearranged ion. *syn*-Brosylate **2b** yielded 2.5% of product that also resulted from a transannular 6,2 hydride shift followed by stereospecific collapse of solvent to yield the epimer of the product from **3b**. The results and product distributions were interpreted in terms of the ionization of **2b** and **3b** to conformationally different epoxycarbinyl cations with rates of interconversion that are slow relative to other product-forming reactions.

The solvolytic reactions of 2-bicyclo[*n*.1.0]alkyl systems **1** have received considerable attention,[1] along with other studies dealing with the nature of cyclopropylcarbinyl cations.[2] The structures of geometrically related epoxycarbinyl cations are also of interest. Whereas the greater electronegativity of oxygen relative to carbon would lead to the prediction that an epoxide group should not stabilize a positive charge on the adjacent carbinyl position as effectively as cyclopropyl for certain geometries, the nonbonding electrons on oxygen can potentially stabilize a positive charge on the carbinyl position by either formation of an oxabicyclobutonium ion or by a favorable lone-pair-electron interaction of the oxygen atom with the carbinyl carbon in the "bisected" geometry.[3]

The nature of the epoxycarbinyl cation clearly is a function of the system from which it is derived. It has been suggested that several acyclic epoxycarbinyl derivatives solvolyze via the intermediacy of oxabicyclobutonium ions.[4] Other acyclic epoxycarbinyl substrates in which the carbinyl carbon is secondary have been reported to solvolyze with participation of the epoxide ring in a manner similar to the participation of cyclopropyl rings in cyclopropylcarbinyl solvolyses.[5] However, several simple acyclic epoxycarbinyl *p*-bromobenzenesulfonate esters have been shown to hydrolyze *without* appreciable anchimeric assistance or participation by the epoxide ring,[6] and preliminary results indicated that the epoxide group is much less effective than a cyclopropane ring in stabilizing a positive charge on the carbinyl position in the solvolytic reactions of *syn*- *and anti*-9-oxabicyclo[6.1.0]non-2-yl *p*-bromobenzenesulfanates (**2b** and **3b**).[7] In this paper, we describe in more detail the hydrolysis reactions of **2b** and **3b**.

Results and Discussion

First-order rate constants for the solvolysis of **2b** and **3b** are provided in Table I, and the relative reactivities of **2b, 3b,** and the related *syn*- and *anti*-2-bicyclo[6.1.0]non-2-yl systems[1a] are provided in Table II. Of significance is the fact that the



1 **2a**, R = H; **b**, R = Bs **3a**, R = H; **b**, R = Bs **4a**, R = H; **b**, R = PNB **5a**, R = H; **b**, R = PNB

rates of solvolysis of **2b** and **3b** are estimated to be ca. 10^6–10^7 times slower than the corresponding rates for their cyclopropylcarbinyl analogues **4b** and **5b**. The slow rates of solvolyses of **2b** and **3b**, relative to **4b** and **5b**, certainly indicate that epoxide rings are not nearly as effective as cyclopropyl rings in stabilizing a positive charge on an adjacent carbon. The syn systems **2b** and **4b** are each significantly more reactive than their corresponding anti epimers **3b** and **5b**, respectively.

A comparison of product distributions from bicyclo[6.1.0]-non-2-yl systems is given in Table III. Whereas the product distributions from **4b** and **5b** are relatively simple,[1a] the product mixtures from **2b** and **3b** are more complex. Yet there are some striking resemblances. (1) Both **2b** and **3b** yield products with net retention of stereochemistry at C-2. Their corresponding cyclopropylcarbinyl analogues **4b** and **5b** each give greater than 99% retention of stereochemistry at C-2. (2) The syn isomers **2b** and **4b** yield significant amounts of suberaldehyde (**6**) and *cis*-3-cyclononenol (**12**), respectively. The similarities of the mechanisms leading to these products are presented in Scheme I. (3) *anti*-Epoxycarbinyl brosylate **3b** yielded a significantly greater amount (17%) of cycloheptenecarboxaldehyde (**7**) than syn isomer **2b**. A possible intermediate in the formation of **7** is the trans-fused bicyclic hemiketal **20** (Scheme II), which corresponds in structure to the trans-fused cyclobutanol **13** from *anti*-cyclopropylcarbinyl *p*-nitrobenzoate **5b**.

There are also some major differences in the solvolysis of *syn*-**2b** and *anti*-**3b**, compared with cyclopropylcarbinyl analogues **4b** and **5b**. (1) Whereas there is no detectable crossover in the product distributions from solvolyses of **4b** and **5b**, at least five products in the solvolyses of **2b** and **3b** are com-

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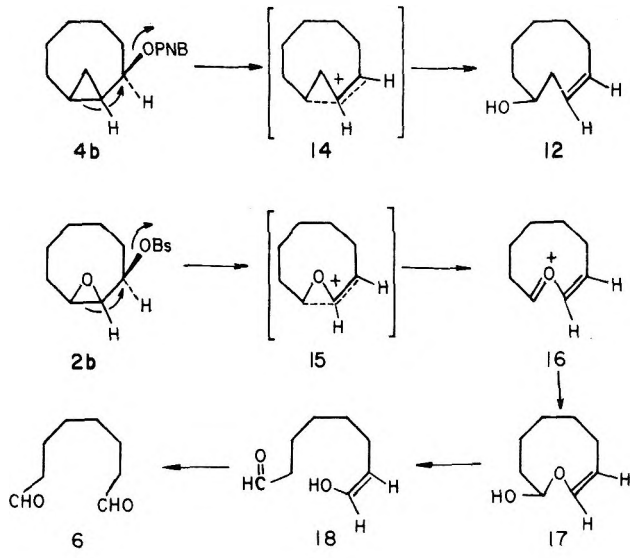
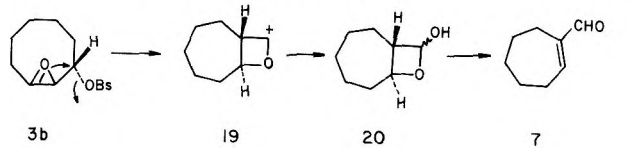
Scheme I

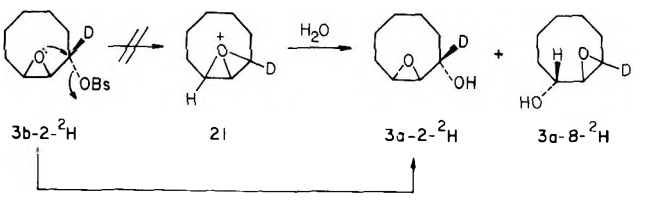


Scheme II



mon. (2) The rates of solvolyses of **2b** and **3b** are ca. 10^6–10^7 times slower than their cyclopropylcarbinyl analogues. (3) Significant amounts of hydride-shift alcohols **8** and **9** and elimination epoxides **10** and **11** are formed from **2b** and **3b.**

Simple primary and secondary acyclic unhindered substrates generally solvolyze to yield almost exclusive inverted product.[8] Those substrates that solvolyze to give products with net retention of stereochemistry at the ionizing carbon often solvolyze either with anchimeric assistance of a neighboring group or by "solvent-unassisted" ionization[9] if the backside of the ionizing carbon is hindered to solvation. Backside participation by nonbonding electrons in **2b** is severely restricted because of geometrical considerations. However, the trans geometry of **3b** is favorable for anchimeric assistance by the nonbonding electrons of the neighboring epoxide group to form an intermediate oxabicyclobutonium ion. Collapse of solvent with the oxabicyclobutonium ion might then give **3a**



and account for the net retention of stereochemistry at C-2.[10] Therefore, **3b**-2-*d* was hydrolyzed. The intermediate oxabicyclobutonium ion **21**, if formed, should lead to scrambling of deuterium between C-2 and C-8 of the major product **3a.** However, the infrared and NMR spectra of the major product were identical with the spectra of **3a**-2-*d.* Participation by the nonbonding electrons of oxygen in the solvolysis of **3b** was therefore ruled out as a major solvolytic pathway.[7]

An interesting aspect of the hydrolysis of **3b** is the formation of 29% of *anti*-9-oxabicyclo[6.1.0]nonan-3-ol (**9**) and no detectable syn isomer **8.** In contrast, hydrolysis of **2b** yielded 2.5% of the syn-alcohol **8** and no detectable anti epimer **9.** This rather stereospecific formation of **8** and **9** from **2b** and **3b,** respectively, is particularly intriguing because reduction of 9-oxabicyclo[6.1.0]nonan-3-one with sodium bis(2-methoxyethoxy)aluminum hydride yielded approximately equal amounts of **8** and **9.**

Table I. First-Order Rate Constants[a] and Activation Parameters[a] for the Solvolysis of 2b and 3b

Compd	Temp, °C	$10^5 k$, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, kcal/mol
		80% Ethanol–Water		
2b	59.8	22.7 ± 0.5	25.3 ± 0.4	0.7 ± 1.3
	49.8	6.64 ± 0.26		
	40.1	1.82 ± 0.07		
	25.0	0.23[b]		
3b	100.3	12.2 ± 0.18	27.3 ± 0.1	−3.7 ± 0.4
	90.2	4.26 ± 0.004		
	80.1	1.40 ± 0.003		
	25.0	0.00089[b]		
		80% Acetone–Water		
2b	50.1	1.65 ± 0.07		
	40.0	0.43 ± 0.01		
3b	100.3	3.63 ± 0.06		
	90.1	1.24 ± 0.02		

[a] Errors are expressed in units of standard deviation. [b] Extrapolated from data at higher temperatures.

Table II. Relative Reactivities of Epoxycarbinyl Substrates 2b and 3b and Cyclopropylcarbinyl Substrates 4b and 5b toward Hydrolysis[a]

Compd	**2b**	**3b**	**4b**[b]	**5b**[b]
k_{rel}	259	1	1.4×10^9	1.6×10^7

[a] The solvolytic reactivity of 2-bicyclo[*n*.1.0]alkyl brosylates was estimated to be ca. 10^9 times greater than that of 2-bicyclo[*n*.1.0]alkyl *p*-nitrobenzoates. This estimate is based on rates of 0.07 s^{-1} for acetolysis of *trans*-2-bicyclo[3.1.0]hexyl tosylate at 25 °C and 8.2×10^{-7} s^{-1} for hydrolysis of *trans*-2-bicycol[3.1.0]hexyl *p*-nitrobenzoate at 100 °C in 80% acetone–water, E. C. Friedrich and S. Winstein, unpublished results. The rates of solvolysis of **2b, 3b, 4b,** and **5b** were extrapolated to 25 °C in a common solvent. [b] Reference 1a.

Two possible mechanisms can explain the formation of anti alcohol **9** from anti brosylate **3b.** One mechanism involves a 3,2 hydride shift, and the second mechanism involves a 6,2 hydride shift (Scheme III). Evidence for a 6,2 hydride shift was provided by the 100-MHz ^{1}H NMR spectrum[11] of the product **25** from solvolysis of *anti*-**3b**-2-*d.* A low-field methylene absorbance at δ 2.35 (1 H) was split into a doublet of triplets (J = 14.5, 4.0, 4.0 Hz). Irradiation of the α hydrogen H_3 (δ 3.9) or epoxide proton H_1 (δ 3.06, d of t, J = 10.5, 4.0, 4.0 Hz) reduced the signal for the low-field proton into a doublet of doublets (J = 14.5, 4.0 Hz). This low-field absorption must, therefore, belong to a proton located at C-2 and was assigned to the anti proton H_{2b} because models indicated that this proton is not located in the shielding cone of the epoxide ring. The syn proton H_{2a} is located in the shielding cone of the ep-

Scheme III

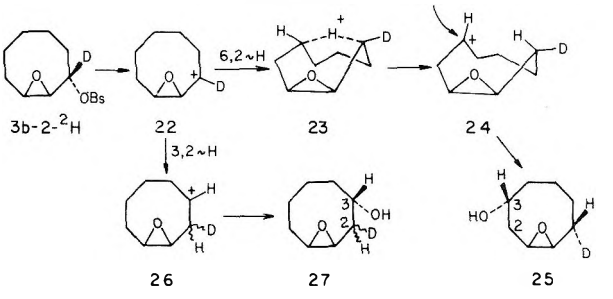


Table III. Product Distributions for Solvolyses of 2b, 3b, 4b, and 5b in 80% Aqueous Acetone

Product[a]	2a	3a	6	7	8	9	10	11
Retention time, min[b]	15.6	28.2	20.6	4.7	31.3[c]	31.3[c]	3.4	2.3
% from 2b	9.1	1.5	52.4	2.8	2.5	~0	28.3	2.5
% from 3b	5.1	36.0	1.9	17.4	~0	28.9	4.9	3.5

Product[d]	4a	5a	12	13
% from 4b[e]	61	<0.3	23	
% from 5b	<0.3	96		4

[a] Triethylamine was used as a buffer. Yields correspond to relative areas of product peaks on a GLC tracing. [b] Analyzed by gas chromatography on a 6 ft × ¼ in., 5% diethylene glycol succinate column. The temperature of the chromatograph oven was programmed from 60 to 160 °C at 3 °C min. [c] Epimers 8 and 9 could not be separated on GLC. However, analysis of the infrared spectra of the solvolysis compounds indicated the lack of contamination (≤ 5%) of the other epimer. [d] Reference 1a. [e] Internal-returned *p*-nitrobenzoate of 12 (16%) was also formed.

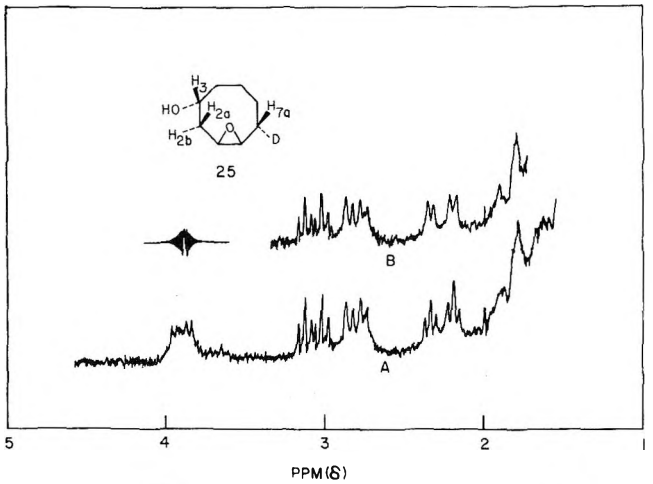


Figure 1. (A) ^{1}H NMR spectrum (100 MHz) of **25**. (B) ^{1}H NMR spectrum of **25** with H_3(*δ 3.9*) decoupled.

oxide group and therefore should absorb at higher field than H_{2b}. The geminal coupling constant of 14.5 Hz is consistent only with structure **25**, containing two protons at C_2. A 3,2 hydride migration is ruled out, since this mechanism would produce product **27** with a deuterium atom located at C_2. The stereospecific anti structure of **25** indicates that collapse of solvent at C_3 is concurrent with a C_6–C_2 hydride shift or is rapid relative to a conformational change of the isomeric ion **24** from the geometry required for hydride shift.[12]

Stereospecific C_6–C_2 hydride migration in the solvolysis of **3b**-*2-d*, *in which the hydride migrates from the backside of* the ionizing center as indicated in **23**, would predict the location of the deuterium atom in **25** to be anti to the epoxide group. This stereochemical assignment was substantiated by analyzing the NMR spectra of **9** and **25**. Models indicate that the syn proton H_{7a} in **25** is in the shielding cone of the epoxide ring and should absorb at high field relative to the anti proton H_{7b}, which is in the deshielding cone of the epoxide ring. A difference in chemical shift between H_{7a} and H_{7b} should amount to ~0.8 ppm.[13] The methylene protons of **9** gave rise to complex absorptions between δ 0.5 and 2.55. Comparison

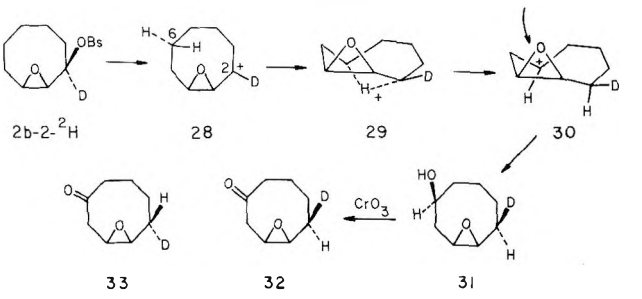
Table IV. NMR Spectral Data for Hydride Transfer Alcohols 9 and 25

Relative area of absorption	δ 9	δ 25
δ 1.85–2.55	2.5	1.6
δ 0.5–1.85	7.5	7.4

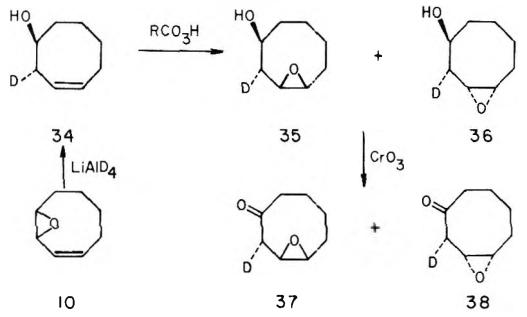
of the relative absorption area between δ 0.5 and 1.85 and δ 1.85 and 2.55 (Table IV) revealed that the position for absorption of the proton that is replaced by deuterium is between δ 1.85 and 2.55. This relatively low-field absorption for this methylene hydrogen suggests that it is located anti to the epoxide group, and therefore the deuterium atom in **25** must also be located anti to the epoxide ring.

We have also obtained evidence that **2b** undergoes a 6,2 hydride shift to yield syn product **8**. This evidence was provided by isolating the hydride-shift product **31** (Scheme IV) of the solvolysis of syn brosylate **2b**-*2-d*. Unfortunately, the NMR spectrum of **31** was too complicated to allow a structure proof in a manner analogous to the assignment of structure **25**. Indirect evidence for the structure of **31** was provided in the following manner. Oxidation of **31** with Jones reagent provided ketone **32**, which possessed an infrared spectrum clearly different from ketone **33** obtained by oxidation of the hydride-shift product **25** of the solvolysis of anti brosylate **3b**-*2-d* (Scheme III). To test if the deuterium atom in **32** was located at C_2, 9-oxabicyclo[6.1.0]nonan-3-one-*2-d* isomers **37** and **38** were synthesized by the route outlined in Scheme V.

Scheme IV



Scheme V



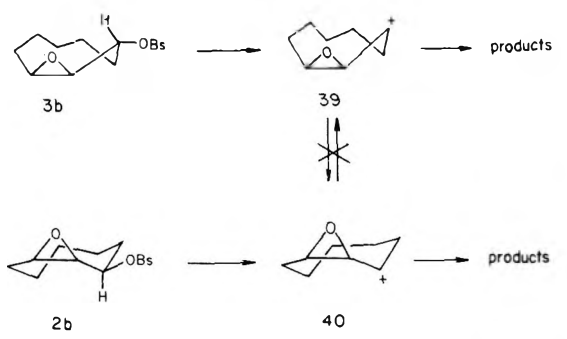
The infrared spectra of both **32** and **33** differed substantially from the infrared spectrum of pure **37** and the spectrum of a mixture of approximately equal amounts of **37** and **38**. Thus, it appears that the deuterium atom in the hydride-shift product from the solvolysis of **2b**-*2-d* is not located to any significant extent at C_2, and consequently a simple 3,2 hydride shift cannot be the major pathway for the hydride-shift product **8**. The fact that the infrared spectrum of **32** was different from that of **33** also indicated that the deuterium atom in **31** was not located in the anti-C_7 position. A mechanism that explains the observations and results in the deuterium located specifically at the syn-C_7 position is outlined in Scheme IV.[14] The stereospecific syn structure of **31** indicates that the collapse of solvent is concurrent with C_6–C_2 hydride migration or is rapid relative to a conformational change of the isomeric ion **30**.

Stereospecific hydride migrations across the top of the ring in the solvolysis of **3b** and across the bottom of the ring in **2b** suggest that the two epimeric esters undergo ionization to conformationally different ions with rates of interconversion that are slow relative to the rates of other product-forming pathways (Scheme VI). The fact that epoxycarbinyl cation **22** underwent substantial rearrangement via hydride migration suggests that the stability of the rearranged cation [9-oxabicyclo[6.1.0]non-3-yl cation (**24**)], in which the cationic center is *not* adjacent to the epoxide group, is *comparable to or greater* than that of **22** (Scheme III).

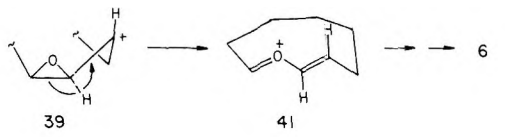
The geometries of the isomeric cations **39** and **40** also help to explain the observed product distributions from the hydrolysis of **2b** and **3b**. The geometry of epoxycarbinyl cation **39** is favorable for migration of the carbon–carbon bond of the epoxide ring to form a trans-fused 2-oxetanyl cation **19** (Scheme II). However, rupture of the carbon–carbon bond of the epoxide ring to give a ring-expanded oxonium ion **41** would require the introduction of a relatively unfavorable trans double bond.[15]

On the other hand, epoxycarbinyl cation **40** possesses a geometry that is favorable for either rupture of the carbon–carbon bond of the epoxide ring to provide a ring-expanded oxonium ion **42** that contains a cis double bond or for migration of the carbon–carbon bond to yield a cis-fused 2-oxetanyl cation **44** (Scheme VIII). The relative stabilities of ions **42** and

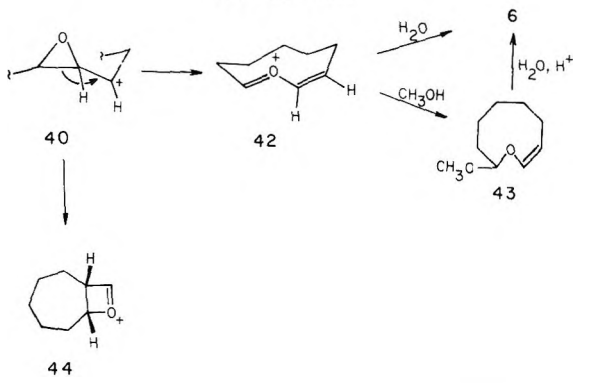
Scheme VI



Scheme VII



Scheme VIII



44 should parallel the stabilities of *cis,cis*-1,3-cyclononadiene and *cis*-bicyclo[5.2.0]non-8-ene, respectively. In the latter series, *cis,cis*-1,3-cyclononadiene is the more stable.[15] Therefore, the rearrangement pathway leading to **42** should be favored over that leading to **44** and accounts for the relatively high yield (52%) of suberaldehyde (**6**) from the hydrolysis of **2b**. The cis nature of the carbon–carbon double bond in **42** was verified by solvolyzing **2b** in methanol, where intermediate **42** is trapped by solvent to yield the stable ketal **43**.[16] The ^1H NMR spectrum of **43** revealed a value of 6 Hz for the olefinic vicincal coupling constant, which is consistent only with a cis double bond in **43**.

The observations that **2b** and **3b** undergo hydrolysis to yield epoxycarbinol products with net retention of stereochemistry at C-2 suggests that the backside of the ionizing center is not readily accessible to solvent. The entropies of activation for solvolysis of **2b** and **3b** in 80% ethanol–water were found to be 0.7 and −3.7 kcal/mol, respectively (Table I). These entropies of activation are ca. 10–18 eu higher than the entropies of activation for solvolysis of the threo and erythro isomers of 3,4-epoxy-2-pentyl brosylate in the same solvent.[6] The latter acyclic brosylates undergo predominant inversion at the ionizing center when hydrolyzed in an acetone–water solution and therefore their more negative entropies of activation may reflect the S_N2 character of the transition states. Consequently, the more positive entropies of activation for solvolysis of **2b** and **3b** may reflect the absence of strong solvation at the backsides of the ionizing centers. This lack of solvation would allow other rearrangement pathways and retention to compete successfully with inversion at the ionizing center. The puckered natures of the medium-sized rings of **2b** and **3b** clearly induce severe geometric constraints on geometries of the intermediates of solvolysis and may also be responsible for the hindrance to solvation of those intermediates.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 257 spectrophotometer, and ^1H NMR spectra were obtained with either an Hitachi Perkin-Elmer R-20A or Varian HA-100 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

anti-9-Oxabicyclo[6.1.0]nonan-2-ol (3a).[17] To a solution of 6.3 g (0.050 mol) of 2-cyclooctenol[18] in 125 mL of methylene chloride, stirred and cooled in an ice–water bath, was added 10.4 g of *m*-chloroperbenzoic acid[19] (85%, 0.051 mol) over a period of ~10 min. The solution was stirred for an additional hour, and the solid precipitate

of *m*-chlorobenzoic acid was removed by suction filtration. The filtrate was washed twice with saturated sodium bicarbonate solution, and the solvent was removed with a rotary evaporator to yield 7.1 g of **3a** as a clear oil: IR (CCl_4) 3600 cm^{-1}; NMR (CCl_4) δ 3.5 (m, 1 H, CHOH), 2.6–3.1 (2 H, protons on epoxide ring).

***anti*-9-Oxabicyclo[6.1.0]nonan-2-yl *p*-Bromobenzenesulfonate (3b).** A solution of 5.6 g (0.022 mol) of *p*-bromobenzenesulfonyl chloride in 16 mL of dry pyridine was cooled in an ice–water bath and 2.0 g (0.016 mol) of **3a** was added.[20] The reaction solution was allowed to stand for 12 h in the refrigerator and was then diluted with ice–water and extracted with ether. The ethereal solution was washed with cold 1 M HCl solution and with saturated sodium bicarbonate solution and was then dried with anhydrous sodium sulfate. The solvent was removed with a rotary evaporator and the residue was filtered through Alumina III with 80:20 pentane–ether. Removal of the solvent yielded 4.86 g (89%) of crude crystalline **3b**, which was recrystallized from benzene–pentane solution to yield 3.3 g of pure **3b**: mp 85.5–86.5 °C; NMR (CCl_4) δ 2.6–3.0 (2 H, epoxide protons), 4.4 (m, 1 H, CHOBs), 7.73 (m, 4 H, aromatic protons).

Anal. Calcd for $C_{14}H_{17}O_4SBr$: C, 46.54; H, 4.74. Found: C, 46.80; H, 4.69.

9-Oxabicyclo[6.1.0]nonan-2-one.[17] To a stirred solution of 3.5 g (0.025 mol) of **3a** in 60 mL of acetone at 0 °C was added 6.75 mL of Jones reagent[21a] over a period of 30 min. The reaction solution was diluted with 700 mL of water and extracted with diethyl ether (3 × 150 mL). The ethereal solution was washed with saturated sodium chloride solution and dried with anhydrous sodium sulfate. Removal of solvent left 3.1 g of oil which was distilled in vacuo to yield 2.1 g (61%) of product: bp 92 °C (0.2 mm) [lit[17] bp 115–116 °C (5 mm)]; mp 94–96 °C [lit[17] mp 92–93 °C] IR (CCl_4) 1725 cm^{-1} (C=O).

***syn*-9-Oxabicyclo[6.1.0]nonan-2-ol (2a).** A mixture of 0.61 g (4.9 mmol) of 9-oxabicyclo[6.1.0]nonan-2-one, 0.70 g (18 mmol) of sodium borohydride, and 25 mL of dry isopropyl alcohol was stirred and heated at 80 °C for 2 h. The reaction mixture was diluted with water and extracted with diethyl ether. The ethereal solution was washed with saturated sodium chloride solution and dried with anhydrous sodium sulfate. The solvent was removed and the residue sublimed at an oil bath temperature of 100 °C (3 mm): yield 0.47 g (78%). GLC analysis (5% diethylene glycol succinate (DEGS) column) revealed that the reduction was ≥98% stereospecific to yield *syn*-**2a**. The material was further recrystallized from pentane–ether solution: mp 89.5–91.0; IR (CCl_4) 3550 cm^{-1}; NMR (CCl_4) δ 2.6–3.0 (3 H, CHOH and epoxide protons), 4.35 (m, 1 H, CHOH).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.31; H, 9.77.

***syn*-9-Oxabicyclo[6.1.0]nonan-2-yl *p*-Bromobenzenesulfonate (2b)** was prepared in 81% yield by the same procedure given above for the preparation of **3b**, mp of **2b**: 117.5–118.5 °C; NMR (CCl_4) δ 2.5–3.0 (2 H, epoxide protons), 5.15 (m, 1 H, CHOBs), 7.75 (m, 4 H, aromatic protons).

Anal. Calcd for $C_{14}H_{17}O_4SBr$: C, 46.54; H, 4.74. Found: C, 46.60; H, 4.80.

Kinetics. A. Solvents. Ethanol (80%)–water and 80% acetone–water solvents were prepared by mixing 4 volumes of organic solvent and 1 volume of water at 25 °C. All solvents were distilled prior to use.

B. Procedures. Approximately 30 mg of *p*-bromobenzenesulfonate ester and 25 μL of triethylamine were dissolved in 25 mL of 80% ethanol–water. An aliquot (2.5 mL) of this solution was sealed in each of 10 ampules. The ampules were placed in a constant-temperature oil bath, thermostated to within ±0.03 °C of the stated temperatures (Table I). At a given time, an ampule was removed, and the absorbance of the solution was measured at 265 nm in a Gilford 2400 spectrophotometer.[21b]

The rates in 80% acetone–water were also determined by the sealed-ampule technique. Approximately 170 mg of *p*-bromobenzenesulfonate was dissolved in 50 mL of 80% acetone–water, and aliquots of the solution (5.5 mL) were sealed in ampules. The ampules were placed in the constant-temperature bath, and at a given time an ampule was removed and 5.0 mL of reaction solution was titrated with standard 0.01 M sodium methoxide–methanol solution to a phenolphthalein end point.

Rate constants for 80% ethanol–water solutions were obtained by nonlinear regression analysis of the data, for each kinetic run, by a Wang 700 calculator computer. The rate constants for 80% acetone–water were obtained by least-squares plots of ln ($V_\infty - V_t$) vs. time, where V refers to titrant volume.

Products from the Hydrolysis of 2b. A solution of 47 mg of **2b**, 100 μL of triethylamine, and 5.0 mL of 80% acetone–water was sealed in an ampule and heated at 60.0 °C for 22.5 h. The reaction solution was diluted with water and extracted several times with diethyl ether. The ethereal solution was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of solvent yielded 16 mg (ca. 85–90%) of oil that was analyzed by gas chromatography on a 5% diethylene glycol succinate column (6 ft × ¼ in). The product distribution and relative GLC retention times are given in Table III.

The products were separated by preparative GLC and identified by comparison of their GLC retention times and infrared and NMR spectra with those of authentic samples where appropriate. Products **10** and **11** were compared with authentic samples prepared by monoepoxidation of 1,3-[22] and 1,4-cyclooctadiene,[23] respectively. Suberaldehyde (**6**) was reduced with lithium aluminum hydride, and the reduction product was compared with authentic 1,8-octanediol.[24] The infrared spectrum of the unsaturated aldehyde **7** was identical with that published for cycloheptenecarboxaldehyde.[25] Products **8** and **9** could not be separated on GLC, but their structures were assigned based on the comparison of their infrared and NMR spectra with the spectra of a mixture of *syn*- and *anti*-9-oxabicyclo[6.1.0]nonan-3-ol prepared by epoxidation of 3-cyclooctenol and by their lithium aluminum hydride reduction to known *cis*- and *trans*-1,3- and 1,4-cyclooctanediols.[12,26]

Products from Hydrolysis of 3b. A solution of 87 mg of **3b**, 100 μL of triethylamine, and 5.0 mL of 80% acetone–water was sealed in an ampule and heated at 100 °C for 43.5 h. The products were isolated and characterized by the same procedure outlined above for the hydrolysis of **2b**. Relative yields are given in Table III.

Preparation of 2a-*2-d*. 9-Oxabicyclo[6.1.0]nonan-2-one (0.8 g) in 10 mL of absolute ethanol was reduced with sodium tetradeuterioborate ($NaBD_4$, 0.25 g)[27] to yield 0.46 g (57%) of product, which was purified by sublimation at 100 °C (3 mm). The NMR spectrum of the product was similar to that for **2a** except that the absorption due to H-2 at δ 4.35 was absent. **2b**-*2-d* was prepared from **2a**-*2-d* by the same procedure for preparation of **2b** above.

2-Cyclooctenone, bp 62 °C (1.5 mm) [lit[28] bp 89 °C (14 mm)], was prepared in 75% yield by Jones oxidation of 2-cyclooctenol.

2-Cyclooctenol-*1-d*. A mixture of 1.04 g of 2-cyclooctenone (8.4 mmol), 353 mg of sodium tetradeuterioborate,[27] and 15 mL of absolute ethanol was stirred at room temperature for 1 h. The reaction was diluted with water and the product extracted into diethyl ether. The ethereal solution was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed to yield 1.4 g of clear oil. GLC analysis of the product on a 7% carbonwax–5% KOH column (6 ft × ¼ in.) showed the presence of ~80% of 2-cyclooctenol-*1-d* and 20% of cyclooctanol.[29]

***anti*-9-Oxabicyclo[6.1.0]nonan-2-ol-*2-d* (3a-*2-d*).** The crude 2-cyclooctenol-*2-d* from above, 1.3 g (containing 20% of cyclooctanol) in 20 mL of methylene chloride, was epoxidized with 2.33 g of 85% *m*-chloroperbenzoic acid by the procedure utilized for the preparation of **3a**, yield 1.8 g of a clear oil. The product was purified by chromatography on 15 g of Alumina III. The cyclooctanol component was eluted from the chromatography column with 20% ether–pentane, and **3a**-*2-d* was eluted from the column with ether. A center fraction contained 0.6 g of **3a**-*2-d* which produced only one peak on gas chromatography (5% diethylene glycol column). The NMR spectrum of the product was similar to that of **3a**, except that the absorption due to H-2 at δ 3.5 was absent. **3b**-*2-d* was prepared from **3a**-*2-d* by the same procedure for the preparation of **3b** above.

3-Cyclooctenol-*anti*-*2-d* (34). 1,3-Cyclooctadiene monoepoxide **10** was reduced with lithium tetradeuterioaluminate ($LiAlD_4$)[27] to **34**.[22] It was assumed that the deuterium was introduced trans to the resulting hydroxyl group.

9-Oxabicyclo[6.1.0]nonan-3-ol (8 and 9). 3-Cyclooctenol (3.90 g, 31 mmol) was epoxidized with 6.2 g of *m*-chloroperbenzoic acid (85%, 31 mmol) by the procedure outlined for the preparation of **3a**. The product was distilled in vacuo: yield 2.56 g (58%); bp (0.4 mm) 100 °C; IR (CCl_4) 3610 cm^{-1}; NMR (CCl_4) δ 3.8–4.3 (2 H, CHOH), 2.75–3.55 (2 H, epoxide protons). The product became semicrystalline upon standing and contained approximately equal amounts of **8** and **9**.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.48. H, 9.80.

Relatively pure (ca. >90%) **8** was prepared by heating 55 mg of a mixture of **8** and **9**, 50 mg of lithium aluminum hydride, and 1 mL of tetrahydrofuran at 65 °C for 1.5 h. GLC analysis of the isolated products (5% diethylene glycol succinate column) indicated that approximately two-thirds of the reactant mixture had been reduced to diols. The remaining epoxy alcohol was isolated by preparative GLC. The infrared spectrum of the material indicated that it consisted of ca. >90% of **8** and ca. <10% of **9**.

9-Oxabicyclo[6.1.0]nonan-3-one. A sample of 59 mg (0.41 mmol) of a mixture of 8 and 9 in 3 mL of acetone was oxidized with 0.10 mL of Jones Reagent.[21a] The reaction solution was diluted with water and extracted with diethyl ether. The ethereal solution was washed with saturated sodium chloride solution and dried with anhydrous sodium sulfate. Removal of solvent left 24.4 mg of crude product (42%). Pure product was isolated by preparative GLC on a 5% diethylene glycol succinate column (6 ft × ¼ in., 100 °C): mp 68–70 °C; IR (CCl_4) 1705 cm^{-1} (C=O). The product was unstable to gas chromatography temperatures above 120 °C.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.27; H, 8.81.

9-Oxabicyclo[6.1.0]nonan-3-ol-*2-d* (35 and 36) was prepared by the epoxidation of **34** with *m*-chloroperbenzoic acid by the procedure outlined above. Relatively pure **35** was prepared by the procedure above for the preparation of **8**.

37 was prepared by Jones oxidation[21] of **35**, and a mixture of **37** and **38** was prepared by the oxidation of a mixture (ca. 50:50) of **35** and **36**.

Methanolysis of 2b. A solution of 2.0 g of **2b**, 2.8 mL of triethylamine, and 40 mL of methanol was sealed in a large ampule and heated at 80 °C for 3 h. The reaction solution was diluted with 500 mL of saturated sodium chloride solution and extracted twice with diethyl ether (total 500 mL). The ethereal solution was dried with anhydrous calcium sulfate and concentrated to a volume of ca. 5 mL by distillation of solvent through a 10-cm fractionating column. The residual solution was analyzed by gas chromatography on a 6 ft × ⅛ in., 10% silicone DC-550 column. The product mixture consisted of 38% of elimination products **10** and **11**,[30] 47% of ketal **43**, and 15% of three unidentified products, presumably the methyl ethers of **2a**, **3a**, and **8**. The major product **43** was separated from the rest by preparative chromatography on a 6 ft × ⅜ in., 10% SE-30 column: isolated yield 0.20 g (ca. 25%); UV (cyclohexane) 215 nm (ε 294); IR (CCl_4) 1650 (C=C) cm^{-1}; IR (CS_2) 760, 767 (CH=CH) cm^{-1}; NMR (CCl_4) δ 1.6 (m, 8 H), 2.1 (m, 2 H, allylic), 3.34 (s, 3 H, OCH_3), 4.48 (t, J = 6 Hz, 1 H, $CHOCH_3$), 4.85 (q, J = 6 Hz, 1 H, $CH{=}CHCH_2$), 6.04 (d, J = 6 Hz, 1 H, $OCH{=}CH$); molecular weight (mass spectrum) 156.

Hydrolysis of 43. A solution of 9 mg of **43**, 0.10 mL of 5% HCl, and 1 mL of 75% acetone–water was allowed to stand at 0 °C for 30 min. The reaction solution was diluted with water and the product was extracted into diethyl ether. The ethereal solution was dried with anhydrous sodium sulfate, and the solution was concentrated to ca. 0.3 mL by removal of solvent. Only one product was detected by gas chromatographic analysis of the residual solution on a 6 ft × ¼ in., 10% apiezon L column. The product was isolated by preparative GLC: yield 3.0 mg (ca. 37% isolated yield) of a clear oil with an infrared spectrum identical with that of suberaldehyde.

Registry No.—**2a**, 31821-36-0; **2a**-*2-d*, 64312-50-1; **2b**, 31186-86-4; **3a**, 31821-35-9; **3a**-*2-d*, 64252-80-8; **3b**, 31186-87-5; **8**, 64312-49-8; **9**, 29077-87-0; **10**, 6690-12-6; **25**, 64252-79-5; **34**, 64252-78-4; **43**, 64252-77-3; 2-cyclooctenal, 3212-75-7; *p*-bromobenzenesulfonyl chloride, 98-58-8; 9-oxabicyclo[6.1.0]nonan-2-one, 57260-84-1; 2-cyclooctenone, 1728-25-2; 2-cyclooctenol-*d*, 64252-76-2; 3-cyclooctenol, 4114-99-2; 9-oxabicyclo[6.1.0]nonan-3-one, 64252-75-1; sodium tetradeuterioborate, 15681-89-7.

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(30) Products **10** and **11** possessed the same retention time on the column used to analyze the product mixture.

Reactions of Epoxides and Carbonyl Compounds Catalyzed by Anhydrous Copper Sulfate

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Received May 17, 1977

Anhydrous $CuSO_4$ and acetone have been used for many years to convert diols to acetonides. We have found that $CuSO_4$/acetone also converts many epoxides directly to acetonides at a convenient rate and in excellent yields. The following observations are pertinent to the mechanism and scope of this reaction: (*E*)- and (*Z*)-2,3-octene oxide each react completely stereoselectively to give the corresponding erythro or threo acetonide, respectively, the (*Z*)-oxide reacting ca. three times faster. In contrast, both (*E*)- and (*Z*)-β-methylstyrene oxide give identical mixtures of erythro (66%) and threo (34%) acetonides; no interconversion of the oxides or the acetonides was detectable. Competition kinetic studies show that para-substituted styrene oxides follow a Hammett relationship of the form $\log (k_X/k_H) = -2.63\sigma^+$, with $r = 0.9994$. Other observations pertaining to the scope, mechanism, and possible extension of these reactions are discussed.

Acetonide derivatives of diols are useful as protected synthetic intermediates, particularly in carbohydrate and steroid chemistry. They are also very well suited for GLC and/or mass spectral analysis of diols, because various geometrical isomers can easily be separated and because the dioxolane ring usually remains intact in the mass spectrometer whereas the diols cleave readily between the hydroxyl groups. Acetonides of diols are also easily prepared by a number of techniques, one of the most convenient being a direct condensation of the diol with acetone in the presence of anhydrous $CuSO_4$.[1-3] During our ^{18}O-tracer studies of the enzyme epoxide hydrase[4] a need arose for converting epoxides directly to acetonides for mass spectral determinations of their ^{18}O content. We found that anhydrous $CuSO_4$ in acetone cleanly and conveniently converts many epoxides directly to their corresponding diol acetonides. This is in contrast to anhydrous zinc[5] or magnesium[5,6] halides which give rearrangement products from epoxides, or anhydrous $FeCl_3$[7] or Me_3SiCl[8] which give chlorohydrin derivatives. In this paper, we describe our studies on the mechanism of the epoxide–acetonide conversion as well as its scope, limitations, and prospects for extension to related reactions.

Results and Discussion

The conversion of an epoxide to a diol and then to an acetonide involves the addition of a molecule of water and its subsequent elimination in the presence of acetone, both reactions being subject to acid catalysis. It occurred to us that it should be possible to effect the overall process as a single step in the presence of a suitable acid catalyst. Our first attempts involved stirring *p*-phenylstyrene oxide **1** and tetradecene 1,2-epoxide **2** in acetone over anhydrous $CuSO_4$; the styrene oxide was quantitatively converted to acetonide within a few hours at room temperature but the alkene oxide remained unchanged after 22 h. This result roughly paralleled the expected behavior of these substrates toward acids, and so kinetic studies were undertaken to explore this possibility. It was found that small amounts of water greatly inhibited the reaction despite their effect in solubilizing the copper reagent. For example, $CuSO_4 \cdot 5H_2O$ dissolves slightly in acetone to produce pale-blue solutions. Epoxides dissolved in these solutions are converted to acetonides extremely slowly, even when stirred over a large excess of finely powdered $CuSO_4 \cdot 5H_2O$. In contrast, anhydrous $CuSO_4$ is not detectably soluble in acetone, and, although acetone decanted after stirring over anhydrous $CuSO_4$ does not convert epoxides to acetonides, epoxides in acetone stirred over anhydrous $CuSO_4$ are readily converted to acetonides. Furthermore, stirred reactions proceed much more rapidly than unstirred reactions, suggesting that the reaction is truly heterogeneous in nature.

In attempting to carry out kinetic studies, we found that, although individual reactions were linear with time, the reproducibility of reaction rates was poor, probably because of the heterogeneous nature of the reaction. However, by incorporating an inert internal standard (naphthalene) we were able to obtain reproducible *relative initial* rates for pairs of epoxides competing for catalyst. Using this approach we found the reactivities of para-substituted styrene oxides to increase in the order $Br < Cl < H < CH_3$. A Hammett plot of $\log (k_X/k_H)$ vs. σ^+ for these substituents yielded a straight line ($r = 0.9994$) with a slope (ρ^+) of −2.63. This amply confirmed our initial suspicions about Lewis acid catalysis and carbonium ionlike intermediates in this reaction.

With aliphatic epoxides the rate of product formation is dependent on the nature of the substitution pattern on the oxirane ring, as shown by the data in Table I. Oxiranes from which a tertiary carbonium ion could be formed react significantly faster than those containing only secondary carbons, and monoalkyl-substituted oxiranes are essentially inert at room temperature, although they react cleanly, if slowly, at elevated temperatures. Although not indicated in Table I, small amounts of the cis and trans isomers of 2,3-epoxytetradecane which occurred as an impurity in **2** were observed to react in a fashion parallel to epoxides **4a** and **4b**. Thus, as already established in homogeneous reactions of epoxides with anhydrous metal ion Lewis acids,[5-7] carbonium ion forming ability plays an important role in governing the reactivity of epoxides in the heterogeneous $CuSO_4$/acetone system as well.

In order to determine the direction of epoxide ring opening, the acetonide derived from ^{18}O-enriched **1**[4] was subjected to mass spectral analysis and compared to unlabeled material. The major fragmentation occurred as shown in **7** with the base peak occurring at *m/e* 72. The origination of this peak as indicated by A in **7** is confirmed by its shift to *m/e* 74 in the mass spectra of the acetonides from both **1**-β,β-d_2 and **1**-^{18}O. The M^+ and $M - CH_3^+$ ions from **7** were, respectively, 25 and 20% of the base peak. In the spectrum of the acetonide from **1**-^{18}O, all three ions (A^+, $M - CH_3^+$, and M^+) contained the same atom-% excess ^{18}O. Therefore, acetonide formation must involve exclusive cleavage of the benzylic C–O bond, which also agrees with previous conclusions about the importance of carbonium ion intermediates.

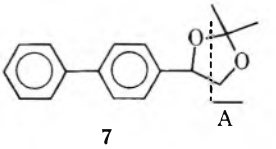

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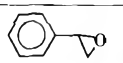
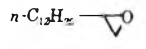
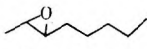
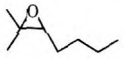
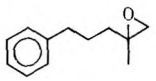
Table I. Relative Reactivities of Aliphatic and Aromatic Epoxides toward $CuSO_4$/Acetone

	Epoxide	Registry no.	Time, h[a]	% conversion
3		96-09-3	≤2	100
2		3234-28-4	22 7 (60 °C)	0 5
4a		23024-54-6	24	50
4b		28180-70-3	24	15–20
5		3776-34-9	24 3	95[c] 40
6		40463-17-0	6 (58 °C)	50

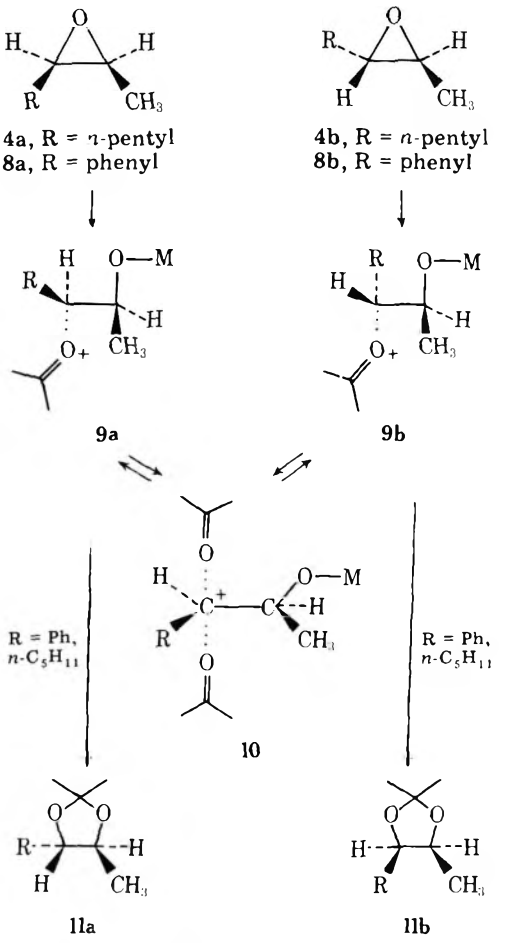
[a] Room temperature unless otherwise noted. [b] Sole product is the corresponding acetonide. [c] About 5% of non-acetonide products with short retention times was formed.

Both (*Z*)- and (*E*)-β-methylstyrene oxide (**8a** and **8b**) react with $CuSO_4$ and acetone to give the same mixture of threo and erythro acetonides (66:34). Acetonides formed under identical conditions from the corresponding erythro or threo diols show no interconversion, even after standing for days at room temperature. The loss of stereochemistry from the epoxides must therefore be due to the formation of a common symmetrical intermediate, such as **10** for example, from which both products could be formed. Interconversion of epoxides was not observed; thus, if it occurred it was much slower than the conversion of **9** to **11** as outlined in Scheme I. In contrast to this situation, acetonide formation from epoxides **4a** and **4b** is completely stereospecific, **4a** giving only threo acetonide and **4b** giving only erythro acetonide. This change of mechanism may be rationalized in terms of the strength of the $Me_2C{=}O{\cdots}C^+$ interaction in intermediate **9**. Thus, because of the greater stability of benzylic carbonium ions, formation of **9** from **8** requires relatively little nucleophilic assistance or solvation from acetone, and interconversion of **9a** and **9b** through **10** is not impeded by a strong $Me_2C{=}O{\cdots}C^+$ interaction. With the aliphatic epoxides, however, oxirane ring opening probably requires much more assistance from the carbonyl oxygen as a nucleophile, such that the strength of the $Me_2C{=}O{\cdots}C^+$ interaction which develops precludes facile interconversion of **9a** and **9b** when R = alkyl. Since the direction of ring opening from **4** is not known, similar arguments would apply to intermediates formed by attack of acetone at the methyl-substituted oxirane carbon; the overall result would of course be the same. The importance of the nucleophilic role of the solvent is also indicated by the fact that even styrene oxide is inert in acetonitrile over $CuSO_4$. Despite the highly polar nature of this solvent, which should help stabilize polar intermediates such as **9**, its low nucleophilicity prevents it from assisting the opening of the oxirane ring. In contrast, styrene oxide in methanol over $CuSO_4$ reacts rapidly to produce only 2-phenyl-2-methoxyethanol. Since $CuSO_4$ dissolves slightly in methanol to give pale blue solutions but does not dissolve noticeably in acetonitrile, it seems unlikely that the difference in reactivity of styrene oxide in these two solvents can be ascribed to attenuation of the catalyst by solvation.

The experiments described above clearly point to the importance of the Lewis acid property of anhydrous $CuSO_4$. However, $CuSO_4$ is also an effective dehydrating agent, much like $CaSO_4$ or $MgSO_4$, and both of these properties are important in its use to form acetonides from diols plus acetone. Many other organic reactions require acid catalysis with dehydrating conditions to shift an equilibrium in a useful direction, but the conversion of diols to acetonides is apparently the only one in which anhydrous $CuSO_4$ is used to advantage. As a start toward exploring the general utility of $CuSO_4$ as a reagent in organic chemistry, we examined its use in convering carbonyl substrates to 1,3-dioxolane and 1,3-dioxane derivatives in diol solvents. The carbonyl compounds were simply dissolved in the diol and stirred over an excess of $CuSO_4$ at room temperature. $CuSO_4$ dissolves in ethylene glycol to give a clear blue solution which converts benzaldehyde and acetophenone to their dioxolane derivatives in 45 and 5% yield, respectively, after stirring for 28 h. Although $CuSO_4$ does not dissolve detectably in propane-1,3-diol, benzaldehyde and acetophenone were converted to their 1,3-dioxane derivatives in yields of 98 and 10%, respectively, after stirring over $CuSO_4$ for 28 h. No attempts have yet been made to increase these yields by the use of larger amounts of $CuSO_4$, longer times, or higher temperatures. Nor is it known if these yields reflect the relative reactivities of the reactants (aldehyde > ketone; dioxane less strained than dioxolane) or an equilibrium under the conditions used. It is also possible that in solubilizing $CuSO_4$ ethylene glycol reduces its Lewis acidity and/or its affinity for water, thus contributing adversely at both the kinetic and thermodynamic levels. A parallel to this exists in the epoxide to acetonide conversion, where small amounts of water greatly decrease the effectivity of $CuSO_4$ as a catalyst despite increasing its solubility in acetone.

Anhydrous $CuSO_4$ can thus serve as a useful catalyst/reagent for several frequently encountered reactions of carbonyl compounds with diols or their epoxide equivalents. The reactions proceed under mild conditions, at rates comparable to those attainable with conventional acid catalysts (e.g., 0.05 M *p*-TsOH), and may be more convenient than other procedures involving azeotropic removal of water to shift an equilibrium.

Scheme I



Experimental Section

Epoxides. Styrene oxide was purchased from Aldrich; all other epoxides were prepared from the corresponding olefins by peracetic acid epoxidation in CH_2Cl_2 buffered with sodium acetate. Their purity was checked by TLC, GLC, and NMR and was >97% in all cases. Tetradec-1-ene and (*E*)- and (*Z*)-2-octene were obtained from Aldrich; 2-methyl-2-heptene (precursor for **5**) was obtained by Wolf–Kishner reduction of 6-methyl-5-hepten-2-one (Aldrich) followed by distillation (bp 120–121 °C); 1-phenyl-4-methylpent-1-ene (precursor for **6**) was obtained by Grignard coupling of 2-phenylethylmagnesium bromide and methallyl chloride in refluxing ether, followed by distillation (bp 90–95 °C, 34 Torr). Para-substituted styrenes were prepared from the corresponding acetophenones by borohydride reduction and dehydration as described previously.[9] *cis*-β-Methylstyrene was prepared by irradiation[10] of a 1% solution of the trans isomer (Aldrich) in benzene containing 2-acetonaphthone (2%) for 8 h under nitrogen in a Rayonet reactor with 350-nm lamps. GLC analysis on a DC-550 column showed that a photosteady state was reached at a cis/trans ratio of 82:18. The sensitizer was removed by filtering the solution through active silica gel. The mixture of isomers obtained after removing the benzene on a rotary evaporator was used *without further purification.*

$CuSO_4$-Catalyzed Reactions. Anhydrous $CuSO_4$ was prepared by *gently* heating the finely powdered pentahydrate in a bunsen flame until it turned very pale blue, cooling in a desiccator, and grinding in a mortar before use. Reactions were stirred at room temperature in screw-cap tubes to keep moisture out. In general, 100 mg of substrate epoxide (or carbonyl compound) was dissolved in 1 mL of acetone (or glycol solvent) and stirred with ca. 50 mg of $CuSO_4$; in more dilute solutions, the reactions proceeded very slowly. In all cases acetonides produced directly from epoxides were identical (GLC) to those produced from the corresponding diol.

Acetonides. The structures of many of the acetonides derived from epoxides **1–6**, **8a**, and **8b** have been confirmed by mass spectroscopy.[4] All of the acetonides mentioned in this study have also been characterized by NMR spectroscopy, and these data are reported here together with their R_f on 0.25-mm silica layers eluted with 10% ethyl acetate in hexane. Each epoxide precursor had essentially the same R_f as its derived acetonide.

2,2-Dimethyl-4-(4′-phenylphenyl)dioxolane: from epoxide **1**, mp 62–65 °C, R_f 0.36; NMR ($CDCl_3$) δ 7.50 (m, arom), 1.49 and 1.55 (CMe_2), 5.10 (t, α-H), 4.30 (t, β-H), 3.72 (t, β-H).

2,2-Dimethyl-4-(*n*-dodecyl)dioxolane: From epoxide **2**, an oil, R_f 0.57; NMR ($CDCl_3$), δ 4.08 (ring CH_2), 3.50 (m, ring CH), 1.38 and 1.44 (CMe_2).

2,2-Dimethyl-4-phenyldioxolane: from styrene oxide, an oil, R_f 0.48; NMR ($CDCl_3$) δ 7.30 (arom), 5.05 (dd, α-H), 4.25 (dd, β-H), 3.66 (t, β-H).

erythro-2,2-Dimethyl-4-pentyl-5-methyldioxolane: from epoxide **4b**, an oil, R_f 0.55; NMR ($CDCl_3$) δ 4.15 (m, ring CH), 1.34 and 1.44 (CMe_2), 1.16 (d, J = 7 Hz, CH_3).

threo-2,2-Dimethyl-4-pentyl-4-methyldioxolane: from epoxide **4a**, an oil, R_f 0.55; NMR ($CDCl_3$) δ 3.60 (m, ring CH), 1.40 (CMe_2), 1.27 (d, J = 7 Hz, CH_3).

2,2,4,4-Tetramethyl-5-butyldioxolane: from epoxide **5**, an oil, R_f 0.62; NMR ($CDCl_3$) δ 3.70 (t, J = 6 Hz, ring CH), 1.10, 1.24, 1.33, and 1.41 (methyls).

2,2,4-Trimethyl-4-(3-phenylpropyl)dioxolane: from epoxide **6**, an oil, R_f 0.41; NMR ($CDCl_3$) 7.14 (s, arom), 3.65 (s, ring CH_2), 2.60 (m, benzylic CH_2), 1.34 and 1.38 (CMe_2), 1.27 (s, CH_3).

erythro-2,2,4-Trimethyl-5-phenyldioxolane: from epoxides **8a** and **8b**, an oil, R_f 0.53; NMR ($CDCl_3$) 7.29 (arom), 5.19 (d, J = 7 Hz, benzylic H), 4.6 (m, ring H), 1.45 and 1.62 (CMe_2), 0.79 (d, J = 6 Hz, CH_3).

threo-2,2,4-Trimethyl-5-phenyldioxolane: from epoxides **8a** and **8b**, an oil, R_f 0.53; NMR ($CDCl_3$) 7.34 (arom), 4.46 (d, J = 9 Hz, benzylic H), 3.92 (m, ring H), 1.50 and 1.55 (CMe_2), 1.25 (d, J = 6 Hz, CH_3).

Kinetic Studies. Solutions of the styrene oxides were prepared (ca. 0.08 *M*) in acetone containing 10 mg/mL naphthalene as an internal standard. Reaction solutions were prepared by combining a 1.0-mL aliquot of each of two such solutions. Reactions were monitored by GLC on either 3% SE-30 (6 ft × ⅛ in. at 85 °C) or 5% DC-550 (10 ft × ⅛ in. at 140 °C). After calibrating the digital integrator on the GLC with two injections of the epoxide/naphthalene solution, 20–50 mg of powdered anhydrous $CuSO_4$ was added and the mixtures were stirred rapidly at room temperature in sealed vials. At 5–10-min intervals, aliquots were analyzed by GLC, and the slope of a plot of epoxide remaining vs. time was taken as the rate of reaction. Due to the heterogeneous nature of the reaction, rates for individual epoxides were poorly reproducible from run to run. However, when two epoxides were competing for the same catalyst, their *relative* rates were quite reproducible. Relative to styrene oxide (1.00) the rates of reaction of *p*-methyl-, *p*-chloro-, and *p*-bromostyrene oxide were 7.65, 0.50, and 0.43, respectively. The Hammett plot of these data is described in the text.

Acknowledgments. This work was supported by National Institutes of Health Grant GM-21784 (to R.P.H.) and an National Science Foundation Undergraduate Research Participation award (M.L.).

Registry No.—**1**, 36099-26-0; **8a**, 4541-87-1; **8b**, 23355-97-7; 2,2-dimethyl-4-(4′-phenylphenyl)dioxolane, 64216-04-2; 2,2-dimethyl-4-(*n*-dodecyl)dioxolane, 64216-03-1; 2,2-dimethyl-4-phenyldioxolane, 52129-03-0; *erythro*-2,2-dimethyl-4-pentyl-5-methyldioxolane, 64216-08-6; *threo*-2,2-dimethyl-4-pentyl-5-methyldioxolane, 64216-07-5; 2,2,4,4-tetramethyl-5-butyldioxolane, 64216-09-7; 2,2,4-trimethyl-4-(3-phenylpropyl)dioxolane, 64235-91-2; *erythro*-2,2,4-trimethyl-5-phenyldioxolane, 64216-06-4; *threo*-2,2,4-trimethyl-5-phenyldioxolane, 64216-05-3; 2-methyl-2-heptene, 627-97-4; 6-methyl-5-hepten-2-one, 110-93-0; 1-phenyl-4-methylpent-1-ene, 15314-20-2; 2-phenylethyl bromide, 103-63-9; methallyl chloride, 563-47-3; *p*-methylstyrene oxide, 13107-39-6; *p*-chlorostyrene oxide, 2788-86-5; *p*-bromostyrene oxide, 32017-76-8; acetone, 67-64-1.

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Aromatic Nucleophilic Substitution. 9.[1] Kinetics of the Formation and Decomposition of Anionic σ Complexes in the Smiles Rearrangements of *N*-Acetyl-β-aminoethyl 2-X-4-Nitro-1-phenyl or *N*-Acetyl-β-aminoethyl 5-Nitro-2-pyridyl Ethers in Aqueous Dimethyl Sulfoxide

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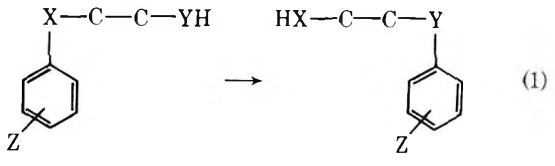
Received February 23, 1977

The kinetics of the base-catalyzed Smiles rearrangements of *N*-acetyl-β-aminoethyl 2-X-4-nitro-1-phenyl [X; NO_2 (**5**), Br (**8**), CN (**9**)] or *N*-acetyl-β-aminoethyl 4-nitro-2-pyridyl ether (**10**) in Me_2SO–H_2O have been studied. For all the substrates studied the anionic σ complexes were spectrophotometrically confirmed to intervene during the rearrangement process, and the rates of rearrangement were found to depend only on the decomposition process of the anionic σ complexes (independent of their formation process). The rate of rearrangement decreases in the order of **10** > **8** > **9** > **5**, and the rate of formation of the anionic σ complex decreases in the order of **5**, **9** > **10** > **8**.

Since the Smiles rearrangement was found by Henriques,[2] it has been developed by many workers, especially by Smiles.[3] The rearrangement is indicated as follows:

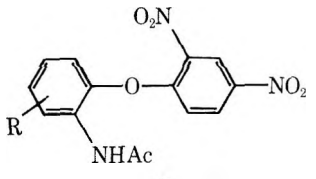


(1)

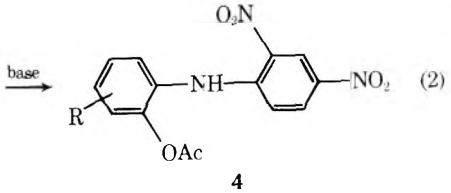
1 **2**

Z; activating group

Although the field has been recently reviewed,[4] there have been few studies on the detailed kinetics of rearrangements because of their mechanistic complexity.[5,6] McClement and Smiles[7] found that the base-catalyzed rearrangement of 2-hydroxy-2′-nitrodiphenyl sulfones to 2-sulfino-2′-nitrodiphenyl ethers is strongly accelerated by a 6-methyl group, which was interpreted to be attributable to its electronic effect, but Bunnett and Okamoto[6] reported that the rate of rearrangement of a 2-hydroxy-2′-nitrodiphenyl sulfone to a 2-(*o*-nitrophenoxy)benzenesulfinic acid is increased about 500 000-fold by the introduction of a methyl, chloro, or bromo substituent in the 6 position and that the origin of acceleration is not electronic but steric. Roberts and deWorms[8] carried out the Smiles rearrangement of 2-acylamidodiphenyl ethers **3** to 2-acyloxydiphenylamines **4** and concluded that the rate of rearrangement decreases with an increasing electron-attracting effect of the substituent in the phenyl or benzoyl group owing to the reduction in availability of the unshared electrons of an amido nitrogen (eq 2). Bernasconi et al.[9] have recently reported the kinetics of the base-catalyzed formation



3



(2)

4

Ac; acetyl or substituted benzoyl

of the anionic σ complex from *N*-(β-hydroxy)ethyl-*N*-methyl-2,4-dinitroaniline and discussed the unusual (reverse) Smiles rearrangement.

We have more recently carried out the base-catalyzed Smiles rearrangement of *N*-acetyl-β-aminoethyl 2,4-dinitrophenyl ether (**5**) to *N*-(β-acetyloxy)ethyl-2,4-dinitroaniline (**7**) in Me_2SO, where the Janovsky complex **6** was spectrophotometrically confirmed to intervene. The results suggested that the rearrangement takes place in two distinct stages and the kinetics in each stage could be spectrophotometrically followed.[10] Skarzewski and Skrowaczewska have recently reported the products in the reaction of various β-(*N*-acylamino)ethoxides or β-(amino)ethoxides with 2,4-dinitrofluorobenzene, which had resulted from an intramolecular Smiles rearrangement with the simultaneous migration of an acyl group from nitrogen to oxygen[11] as we already found in a similar phenomenon.[10] They could not, however, evidence the intervention of anionic σ complexes.

This paper reports the kinetics of the formation and decomposition of the anionic σ complexes in the base-catalyzed Smiles rearrangement of *N*-acetyl-β-aminoethyl nitrophenyl or nitropyridyl ethers and the effect of substituents in the 2 position of the phenyl group on the rate of rearrangement. On the basis of the kinetics, the decomposition of anionic σ complexes to products has been found to be rate determining in the rearrangement, which is interestingly independent of the formation of complexes and greatly contrasted with the results of the previous work.[6-8]

Results

Anionic σ Complexes in Base-Catalyzed Smiles Rearrangements of *N*-Acetyl-β-aminoethyl 2,4-Dinitro-1-phenyl (5), 2-Bromo-4-nitro-1-phenyl (8), 2-Cyano-4-nitro-1-phenyl (9), and 5-Nitro-2-pyridyl (10) Ethers in Me_2SO. The anionic σ complex [λ_{max} 347 (ε 14 300), 359 (ε 13 800), and 506 nm (ε 28 000)] formed in the tertiary-butanolic $KOC(CH_3)_3$-catalyzed rearrangement of **5** to **7** in Me_2SO was already described in the previous paper.[10] Figure 1 shows the spectral change when 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ is added to a Me_2SO solution of **8** (1.93×10^{-5} M). Curve d coincided in position and shape with the spectrum of **12** [λ_{max} 481 nm (ε 34 700)] obtained when excess tertiary-butanolic $KOC(CH_3)_3$ was added to a Me_2SO solution of *N*-(β-acetyloxy)ethyl-2-bromo-4-nitroaniline (**13**) under the same condition. Curve b can be attributed to the anionic σ complex **11**, because the stopped-flow method gave the same absorption spectrum as curve b when KOH was added to a Me_2SO–H_2O (96:4, v/v) solution of **8** (KOH 0.40×10^{-2} M; **8**

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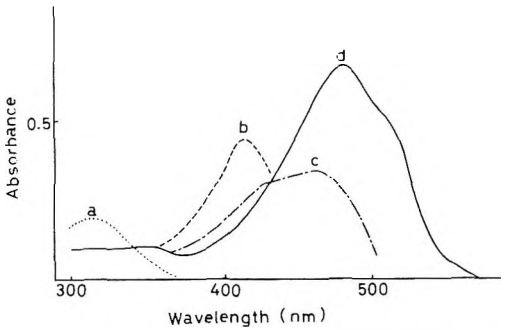
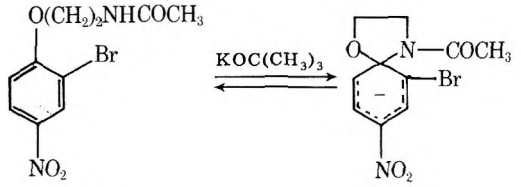
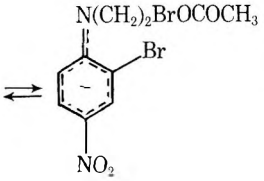


Figure 1. Absorption spectra relevant to the reaction of **8** with tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO at 25 °C. (a) **8** (1.93×10^{-5} M); b, c, and d monitered to the shorter wavelength region at 430, 500, and 600 nm, respectively, immediately after addition of 50 equiv of tertiary butanolic $KOC(CH_3)_3$ (chart speed 100 nm/1.67 min).

2.40×10^{-5} M) at the ionic strength (μ) of 0.1 ($KClO_4$) at 25 °C (Figure 2[12] and about the saponification of **12** refer to ref 16). Furthermore, the absorption spectrum of the anionic σ



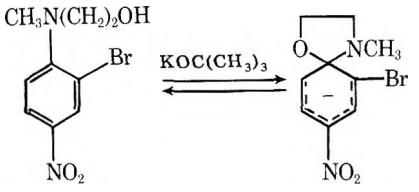
8 **11**



(3)

12

complex **15**, which is formed on addition of 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ to a Me_2SO solution of **14** and very



(4)

14 **15**

stable,[9,10] is similar in position and shape (λ_{max} 397 nm) to curve b. Hosoya et al.[13] already reported that the shape of absorption spectra of such complexes as **11** or **15** is little affected by the group attached to an amino nitrogen. These results, therefore, clearly indicate that curve b in Figure 1 is characteristic of the complex **11**.

The absorption spectra of the reaction of **9** (2.47×10^{-5} M) with 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO are shown in Figure 3, where curve b is attributed to the anionic σ complex **16** [λ_{max} 412 and 420 (sh) nm][9,10,13] and curve d to **17** [λ_{max} 475 nm (ϵ 30 600)]. These assignments were confirmed in a similar manner as with **8** (eq 4 and 6).

The reaction of **10** (2.68×10^{-5} M) with 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO gave only the spectrum of **22** [λ_{max} 461 nm (ϵ 28 400)] even at the faster chart speed, which is the same as that [λ_{max} 462 nm (ϵ 27 100)] obtained in the reaction of 2-[*N*-(β-acetyloxy)ethyl]amino-5-nitropyridine (**23**) with 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO. However, the stopped-flow method gave a similar spectrum

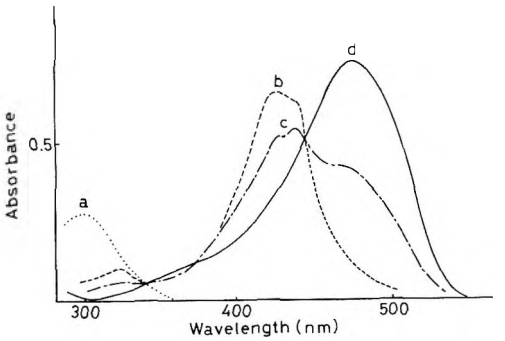
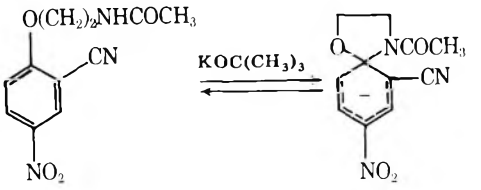
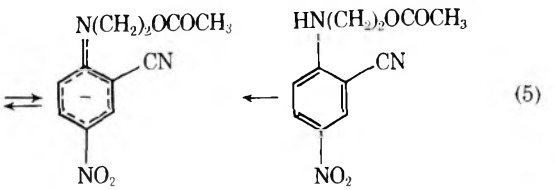


Figure 3. Absorption spectra relevant to the reaction of **9** with $KOC(CH_3)_3$ in Me_2SO at 25 °C: (a) **9** (2.47×10^{-5} M); b and c monitered to the shorter wavelength region at 500 and 600 nm, respectively, immediately after addition of 50 equiv of tertiary butanolic $KOC(CH_3)_3$ (chart speed 100 nm/1.67 min); (d) 5 min after addition of 50 equiv of tertiary butanolic $KOC(CH_3)_3$.

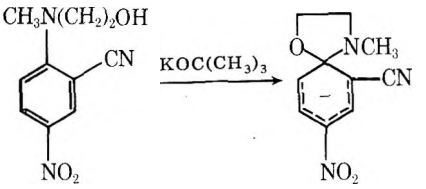


9 **16**



(5)

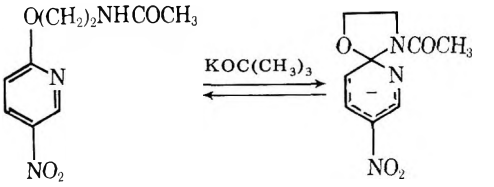
17 **18**



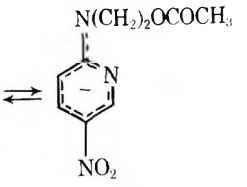
(6)

19 **20**

(λ_{max} 400 nm) to that [λ_{max} 406 nm (ϵ 20 900)] of the complex **25** formed in the reaction of 2-[*N*-(β-hydroxy)ethyl-*N*-



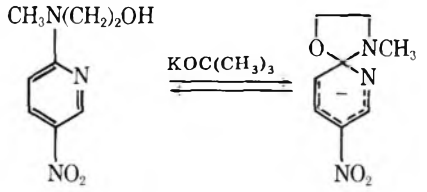
10 **21**



(7)

22

methyl]amino-5-nitropyridine (**24**) with 100 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO under the same condition as with **10** (eq 8). These results indicate that **21** intervenes during the course of the reaction. From these results, we have found that the reaction of the substrate (**5**, **8**–**10**) with



24 25 (8)

$KOC(CH_3)_3$ in Me_2SO occurs in two observable stages: formation and decomposition of the anionic σ complex, the latter corresponding to the rearrangement.

Our observations will be shown later to be consistent with the mechanism of Scheme I, where hydroxide ion is used as a base.

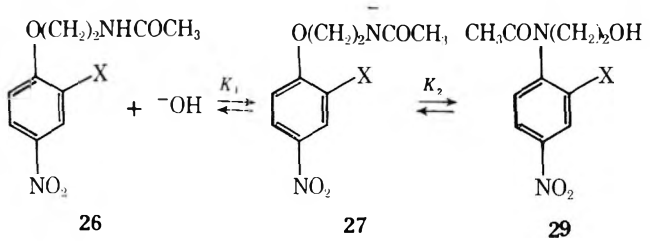
Rate Equations of Rearrangements. We rewrite Scheme I in a fashion more useful for quantitative discussions in Scheme II.

In Scheme II two rates are measurable (those of the formation and decomposition of **28**). Equations 10 and 13a pertain to proton abstraction equilibria which are rapidly established. Although **26**, an amide, functions as a weak acid,[14] the process (eq 10) occurs to some extent in strongly basic media as shown in the work of Hine and Hine[15] (in the case of **8** and **10**, [**27**]/[**26**] becomes 0.78 and 0.56, respectively, under the condition of $[^-OH] = 6 \times 10^{-3}$ M, based on the data as will be shown later). K_1K_2, therefore, is anticipated to be very large. K_5 can be resonably assumed to be very small. Under the present condition, therefore, the equilibria (eq 10 and 11, and 13a) lie almost entirely on **28** and **30**, respectively.

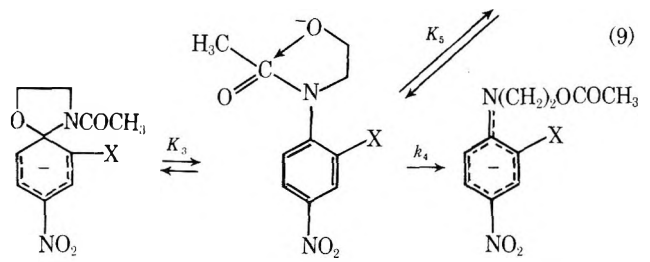
As will be shown later, the earlier stages (eq 10 and 11) are much faster than the later ones (eq 12 and 13), and, therefore, the earlier ones can be dealt with as equilibria in treatment of the kinetics of the later ones.

If the possibility that the substrate may be split among

Scheme I



26 27 29



28 30 31

Scheme II

$$26 + {}^-OH \underset{}{\overset{K_1}{\rightleftharpoons}} 27 \quad (10) \qquad 27 \underset{k_{-2}}{\overset{K_2}{\rightleftharpoons}} 28 \quad (11)$$

$$28 \overset{K_3}{\rightleftharpoons} 30 \quad (12) \qquad 30 \overset{K_5}{\rightleftharpoons} 29 \quad (13a)$$

$$30 \xrightarrow{k_4} 31 \quad (13b)$$

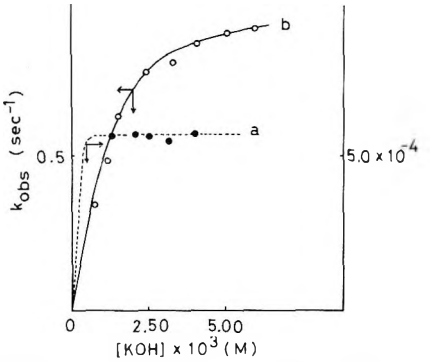


Figure 4. Relationship between k_{obsd} and [KOH] in the reactions of **5** (a, - - -) and **10** (b, —) with KOH in 96% Me_2SO at 25 °C: $[5]_0$ 3.0×10^{-5} M; $[10]_0$ 4.4×10^{-5} M; μ 0.1 ($KClO_4$).

27–30 is taken account of, for the rate of rearrangement the most general expression is as follows:

$$\text{rate} = k_{obsd}[\mathbf{26}]_{st} = \frac{k_4K_1K_2K_3[^-OH][\mathbf{26}]_{st}}{1 + K_1K_2K_3K_5 + (K_1 + K_1K_2 + K_1K_2K_3)[^-OH]} \quad (14)$$

Rearranging eq 14, one can derive

$$\frac{1}{k_{obsd}} = \frac{1 + K_1K_2K_3K_5}{k_4K_1K_2K_3[^-OH]} + \frac{1 + K_2 + K_2K_3}{k_4K_2K_3} \quad (15)$$

On the basis of plots of $1/k_{obsd}$ against $1/[^-OH]$, one can obtain $k_4K_1K_2K_3/(1 + K_1K_2K_3K_5)$ and $k_4K_2K_3/(1 + K_2 + K_2K_3)$ from slopes and intercepts. In the special case in which $(K_1 + K_1K_2 + K_1K_2K_3)[^-OH] \gg 1 + K_1K_2K_3K_5$, eq 14 simplifies to eq 16.

$$k_{obsd} = \frac{k_4K_2K_3}{1 + K_2 + K_2K_3} \quad (16)$$

Equation 16, therefore, indicates that the rate of rearrangement is zero-order in $[^-OH]$ under the above-described condition (Figure 4a). In the cases in which this condition is not fulfilled (Figure 4b), the curvilinear dependence of k_{obsd} on $[^-OH]$ will be found and consequently, k_{obsd} can be evaluated by the extrapolation of $1/[^-OH]$ to the intercept in the linear plot of $1/k_{obsd}$ against $1/[^-OH]$ (eq 15) (Figure 5[12]).

In all runs, the base (KOH) was in a large excess over the substrate concentration, which assures pseudo-first-order kinetics throughout.[16] Our data are summarized in Table I with activation parameters. In the case of **8** and **10** was found the curvilinear dependence of k_{obsd} on $[^-OH]$, and, consequently, the rate constants were obtained by use of inversion plots and found to be 3.58×10^{-2} and 1.10 s^{-1} for **8** and **10**, respectively (Figure 5[12]). Table I shows that the relative rate of rearrangement at 25 °C is 1, 62, 83, and 1900 for **5**, **8**, **9**, and **10**, respectively, and that it increases with decreasing electron-attracting effect of an ortho substituent, except for **10**. The order is reversed in the base-catalyzed rearrangement of 2-hydroxy-5-methyl-(2′-R-4′-nitro)diphenyl sulfone [R; NO_2 (very rapid) > C_6H_5CO > CO_2Na > H (very slow)] carried out by Galbraith and Smiles.[17] They concluded that their results were due to the easy formation of an anionic σ complex or a transition state by the electron-attracting effect of a 2′-R-group, even though it was not clear by way of which state the rearrangement proceeded. The result for **10** can be considered to be due to the absence of steric hindrance.

Thus, in our case it has been made clear that the rate of rearrangement increases, as an ortho substituent is less electron-attracting and less bulkier, which is different from the results of Bunnett and Okamoto,[6] too.

Rate Equations of Anionic σ Complex Formation (eq 10 and 11). In order to clarify whether the origin of the change

Table I. Kinetic Data Relevant to the Rearrangement

Substrate	Temp, °C	10^3 [KOH], M	k_{obsd}, s^{-1}	Rel rate	$\Delta H^{\ddagger}$, kcal·mol	$\Delta S^{\ddagger}$, e.u.
5[b]	20	6.0	3.28×10^{-4} [f]			
	25	1.2	5.84×10^{-4}			
		2.0	5.71×10^{-4}			
		2.4	5.76×10^{-4}	1	16.6	−18.1
		3.2	5.60×10^{-4}			
		4.0	5.94×10^{-4}			
	30	6.0	8.43×10^{-4} [f]			
	40	6.0	2.16×10^{-3} [f]			
8[c]	20	1.6	1.73×10^{-2}			
		2.4	1.83×10^{-2}			
		3.2	1.87×10^{-2}			
		4.0	1.96×10^{-2}			
		5.0	1.96×10^{-2}			
		6.0	2.00×10^{-2}			
	25	1.6	2.60×10^{-2}			
		2.4	2.98×10^{-2}			
		3.2	3.00×10^{-2}			
		4.0	3.06×10^{-2}	62	16.0	−11.5
		5.0	3.24×10^{-2}			
		6.0	3.27×10^{-2}			
	35	1.6	6.17×10^{-2}			
		2.4	6.76×10^{-2}			
		3.2	6.90×10^{-2}			
		4.0	7.30×10^{-2}			
		5.0	7.46×10^{-2}			
		6.0	8.06×10^{-2}			
9[d]	20	6.0	2.82×10^{-2} [f]			
	25	0.8	4.68×10^{-2}			
		1.6	4.83×10^{-2}			
		2.0	4.71×10^{-2}			
		2.8	4.93×10^{-2}	83	15.4	−13.1
		3.6	4.73×10^{-2}			
		4.0	4.72×10^{-2}			
	30	6.0	6.62×10^{-2} [f]			
	40	6.0	1.64×10^{-1} [f]			
10[e]	25	1.6	6.25×10^{-1}			
		2.4	7.69×10^{-1}			
		3.2	7.94×10^{-1}			
		4.0	8.55×10^{-1}	1900		
		5.0	8.93×10^{-1}			
		6.0	9.09×10^{-1}			
	35	1.6	1.27			
		2.4	1.60			
		3.2	1.75			
		4.0	2.06		16.6	−1.2
		5.0	2.05			
		6.0	2.07			
	45	1.6	2.50			
		2.4	3.40			
		3.2	3.82			
		4.0	4.24			
		5.0	4.27			
		6.0	4.60			

[a] Base KOH; μ 0.1 ($KClO_4$); solvent 96% Me_2SO (v/v). [b] $[5]_0$ 3.0×10^{-5} M. [c] $[8]_0$ 2.3×10^{-5} M. [d] $[9]_0$ 2.6×10^{-5} M. [e] $[10]_0$ 4.4×10^{-5} M; measured by means of a stopped-flow method. The accuracy of k_{obsd} is within ±0.25−. [f] All k_{obsd} are an average of at least triplicate measurements.

in the rate constant is electronic or steric, the kinetics of formation of anionic σ complexes were carried out under similar conditions to those in the measurements of the rates of rearrangement.

In the case of **5** and **9** the rates of formation of the anionic σ complexes were too fast to be followed by the stopped-flow spectrophotometric method, while in the case of **8** and **10** the stability of formed complexes was moderate enough for rates to be measured. From eq 10 and 11, the pseudo-first-order rate constant for the attainment of equilibrium is the sum of the first-order rate constants for the forward and reverse reactions. As a general rate expression, one can derive eq 17,

$$k_{\psi} = k_{-2} + \frac{k_2 K_1[^-OH]}{1 + K_1[^-OH]} \tag{17}$$

where k_2 and k_{-2} are the rate constants for the forward and reverse reactions of eq 11, respectively. Therefore, the plot of k_{ψ} against $[^-OH]$ would give a curvilinear dependence unless $K_1[^-OH] \gg 1$. This is the case with **8** and **10**, where k_{-2} could be obtained from the extrapolation of $[^-OH]$ to the intercept in the above-described plot (Figure 6[12]). Once k_{-2} is obtained, eq 18 could be easily derived. Therefore, from the slope and intercept in the plot of $1/(k_{\psi} - k_{-2})$ against $1/[^-OH]$ (eq 18), k_2 and K_1 could be evaluated (Figure 7[12]). Relevant data are summarized in Table II. K_1s in Table II is considered to be resonable from a consideration of the work of Hine and Hine.[14,15]

$$\frac{1}{k_{\psi} - k_{-2}} = \frac{1}{k_2} + \frac{1}{k_2 K_1[^-OH]} \tag{18}$$

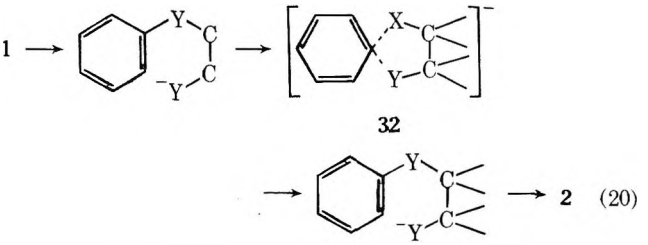
Discussion

Formation of Anionic σ Complexes. The difference between k_2s in Table II may result from the electron-attracting and stereoelectronic characters of pyridyl nitrogen. The values of K_1 are considered to be reasonable on the basis of the fact that a 2-Br group is a little more electron attracting than a pyridyl nitrogen from a consideration of the pK_as of 2-bromophenol[18] and 2-hydroxypyridine.[19] Although in the case of **5** and **9** k_2 and K_1 could not be obtained, K_1 and K_2 can be expected to be at least larger than 131 and 11, respectively, because the rates of formation of anionic σ complexes are too fast to be followed by a stopped-flow spectrophotometric method.

Rates of Rearrangement. As in both cases (**5** and **9**), K_2 is considered to be much larger than 1; therefore, one can approximate eq 16 as follows:

$$k_{obsd} = \frac{k_4 K_3}{1 + K_3} \tag{19}$$

Even in the case of **8** and **10**, K_2s are evaluated to be much larger than 1 as described in the preceding section, and, therefore, eq 19 still holds. Equation 19 indicates that the rate of rearrangement depends only on the decomposition of an anionic σ complex, independent of its formation. This result is very interesting, because all previous work put emphasis on the formation of the transition states **32** and **33**.[3,6,17] Several pathways are possible for the conversion of **1** to **2**; the nucleophilic function, YH, may be ionized with substitution proceeding via the transition state **32** (eq 20). On the other



(20)

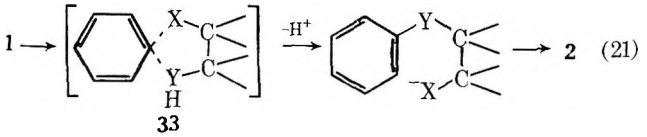
hand, prior ionization is not always required, and the rearrangement may proceed in a concerted fashion through the transition state **33** (eq 21). In certain systems the rearrangement proceeds through such a stabilized intermediate as **28**.[4a] If the rate of rearrangement, however, depends only on the decomposition process of a stabilized intermediate (anionic

Table II. Kinetic Data Relevant to the Formation of Anionic σ Complexes[a]

	k_2, s^{-1}	k_{-2}, s^{-1}	K_1, M	K_2	10^3 [KOH], M	k_ψ
					0.8	(2.19 ± 0.10) × 10
					1.2	(2.76 ± 0.10) × 10
					1.6	(3.20 ± 0.10) × 10
8	1.18 × 10^2	1.10 × 10	1.31 × 10^2	1.07 × 10	2.4	4.03 ± 0.09) × 10
					3.2	(4.54 ± 0.16) × 10
					4.0	(5.10 ± 0.13) × 10
					5.0	(5.69 ± 0.15) × 10
					6.0	(5.83 ± 0.17) × 10
					0.8	(5.44 = 0.31) × 10
					1.2	(7.46 ± 0.58) × 10
					1.6	(8.96 ± 0.35) × 10
10	5.99 × 10	1.20 × 10	9.33 × 10	4.50 × 10	2.4	(1.21 ± 0.10) × 10^2
					3.2	(1.57 ± 0.09) × 10^2
					4.0	(1.86 ± 0.04) × 10^2
					5.0	(2.00 ± 0.03) × 10^2
					6.0	(2.12 ± 0.01) × 10^2

[a] $[8]_0$ 2.4 × 10^{-5} M; $[10]_0$ 4.4 × 10^{-5} M; solvent 96% Me_2SO (v/v); base KOH; μ 0.1 ($KClO_4$); measurements at 416 (8) and 400 nm (10). k_ψs represents average values of four or five determinations.

σ complex), the configuration of A or B would play an important role in the decomposition, because Table I indicates that the difference in rate constants would depend on the

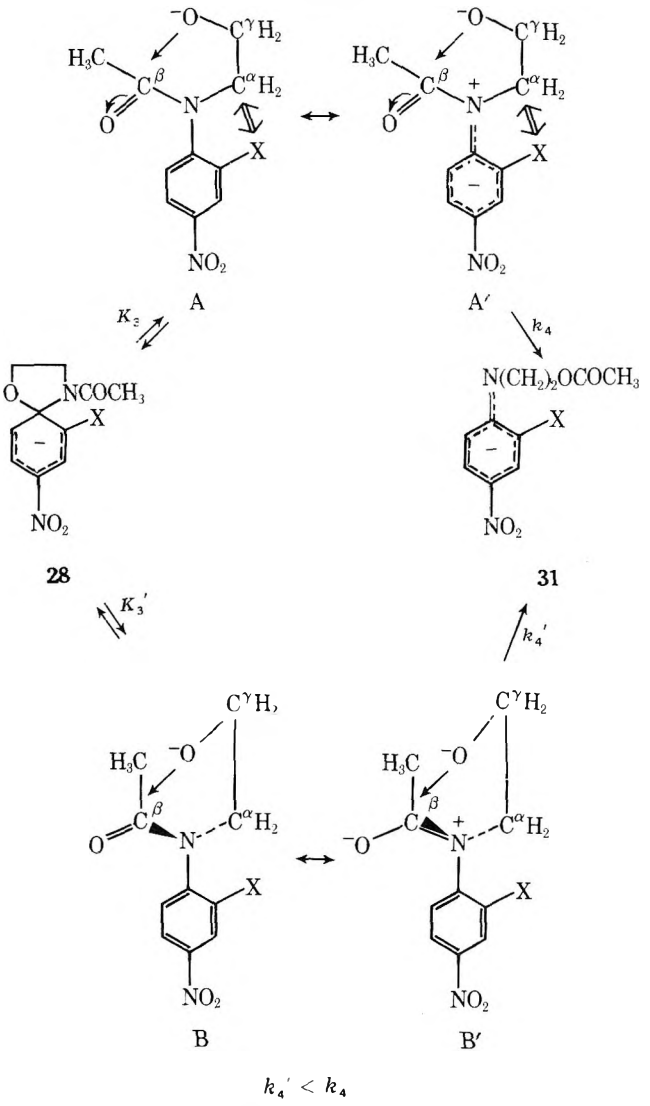


33

entropy of activation rather than on the enthalpy of activation. The conspicuous feature that the entropy of activation for **10** is much larger than those for other substrates indicates that the steric factor is very important in the rearrangement.

These results are clearly explained below. In **28** the five-membered heterocycle is perpendicular to the aromatic ring in the preferred configuration. In the case of **10**, the equilibrium (K_3) lies on configuration A, viz., K_3 is larger, in which the conjugation of the lone-pair electrons of the amino nitrogen with the pyridine ring is larger because of the coplanarity of the C^α–N–C^β group with the pyridine ring owing to the absence of the steric interference by an X group, and the free rotation of the N–C^α and C^α–C^γ bonds is possible (Scheme III). Therefore, in the transition state (k_4 stage) the rotation of the five-membered heterocycle about the C_1–N bond, which is formed by the attack of the oxyanion upon the carbonyl carbon, is considerably free. Furthermore, in configuration A the attack of the oxyanion is concerted with the

Scheme III. Interpretative Scheme Indicating the Influence of an Ortho Substituent



polarization of carbonyl group because of the predominant resonance (A ↔ A′).

On the contrary, in the case of **5**, **9**, and **8**, the C^α–N–C^β group forms a certain angle with the benzene ring by the steric interference of an X group such that the hydrogen atom in the 6 position is put between the C^β=O and C^β–CH_3 bonds (configuration B); the lone-pair electrons of the amino nitrogen is conjugated with the aromatic ring to a lesser extent than in configuration A. With **5** the rotation of the N–C^α bond is completely inhibited and the free rotation of the C^α–C^γ bond is not possible, while with **9** and **8** the former rotation is not completely inhibited and the latter rotation is possible. These circumstances are reflected in the difference among the entropies (Table I). Furthermore, the attack of oxyanion on the carbonyl carbon is not completely concerted with the polarization of the carbonyl group owing to the partial resonance (B ↔ B′), viz., $k_4' < k_4$.

In conclusion, it is considered that the difference in the rate constant in the rearrangement would result mainly from the steric interference of 2-X group.

Experimental Section

Capillary melting points are uncorrected. NMR spectra were recorded with a Varian A-60D spectrometer according to the previous procedure.[20] Elemental analyses were performed at the Microanalytical Center of Gunma University. UV and visible spectra were measured with a Hitachi-124 UV–vis spectrophotometer. Molecular extinction coefficients and absorption maxima were determined in

Me_2SO. The reaction rates were followed conventionally and with a Union RA-1200 rapid-reaction analyzer (Union Giken Co., Ltd.). Chromatographic columns and TLC plates were prepared with Wako Gel C-200 (silica gel) and B-10 (silica gel), respectively.

***N*-Acetyl-β-aminoethyl 2,4-Dinitro-1-phenyl Ether (5).** The ether **5** was prepared according to the previous procedure.[10] The NMR and visible spectra of **5** and its spiro complex **6**, corresponding in structure to **11**, were described in the previous paper.[10] The preparation of *N*-(β-acetyloxy)ethyl-2,4-dinitroaniline (**7**) and its anion corresponding in structure to **11** and their NMR and visible spectra were already described.[10] The preparation of *N*-(β-hydroxy)ethyl-*N*-methyl-2,4-dinitroaniline and its spiro anionic σ complex corresponding in structure to **15** and **20**, respectively, were reported by Bernasconi et al.[9]

***N*-Acetyl-β-aminoethyl 2-Bromo-4-nitro-1-phenyl Ether (8).** 4-Nitrofluorobenzene (NFB), which is a yellowish oil [bp 95–97 °C/22 mm (lit.[21] 98–100 °C/18 mm)], was prepared according to the procedure of Olah et al.[21] in 68% (25 g) yield by the reaction of 25 g (0.260 mol) of commercial fluorobenzene with the mixed acid of 16 g of HNO_3 (*d* 1.41) and 56 g of concentrated H_2SO_4 at −10 °C. 2-Bromo-4-nitrofluorobenzene (BNFB) was obtained in a 64% yield (10 g) by brominating NFB according to the general procedure of Derbyshire and Waters:[22] white crystals, mp 57.5–58.5 °C (lit.[23] 58–59 °C). To a solution of 3.86 g (0.0375 mol) of *N*-acetylethanolamine (NAEA) in 100 mL of dioxane was added 0.975 g (0.025 g-atom) of potassium, and the mixture was refluxed until the potassium was completely dissolved. Upon cooling the mixture to room temperature, 5.0 g (0.023 mol) of BNFB was added and stirred for 30 min. Then, the mixture was poured onto ice water and extracted with chloroform. After the chloroform was distilled off, the residue was seperated on a chromatographic column (silica gel, benzene–acetone 10:3, v/v) and recrystallized from benzene–ligroin: yield 29% (2.0 g); mp 124.5–125.5 °C; UV λ_{max} 317 nm (ϵ 9.18 × 10^3).

Anal. Calcd for $C_{10}H_{11}BrN_2O_4$: C, 39.62; H, 3.66; N, 9.24. Found: C, 40.04; H, 3.73; N, 9.32.

***N*-Acetyl-β-aminoethyl 2-Cyano-4-nitro-1-phenyl Ether (9).** 2-Chloro-5-nitrobenzonitrile was obtained in a 75% yield [25 g, yellow oil, bp 119–122 °C/0.6 mm (lit.[24] 119–122 °C/0.6 mm)] by the reaction of 25 g (0.181 mol) of o-chlorobenzonitrile with 86 mL of fuming HNO_3 (*d* 1.5) according to the procedure of Wilshire.[24a] 2-Chloro-5-nitrobenzonitrile was also changed to 2-fluoro-5-nitrobenzonitrile (FNBN) in a 78% yield according to the procedure of Wilshire.[24a] **9** (pale-yellow crystals) was prepared from FNBN and NAEA in a 23% yield in a similar manner as with **6**: mp 132–133.5 °C; UV λ_{max} 303 nm (ϵ 1.14 × 10^4).

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.88; H, 4.53; N, 16.88.

***N*-Acetyl-β-aminoethyl 5-Nitro-2-pyridyl Ether (10).** 2-Aminopyridine was changed to 5-nitro-2-aminopyridine by use of a mixed acid of HNO_3 and H_2SO_4 in about 70% yield, which was further diazotized and hydrolyzed to 5-nitro-2-hydroxypyridine. 5-Nitro-2-hydroxypyridine was chlorinated to 5-nitro-2-chloropyridine with PCl_5 and $POCl_3$ according to the method of Phillips.[25] The yield including diazotization, hydrolysis, and chlorination was 27%. 5-Nitro-2-chloropyridine was fluorinated to 5-nitro-2-fluoropyridine [bp 86–87 °C/7 mm (lit.[26] 86–87 °C/7 mm)] in a 81% yield according to the procedure of Finger and Starr,[26] except for the reaction temperature of 120 °C and the reaction time of 8 h. **10** (white crystals) was prepared in a 36% yield in a similar manner as with **6**: mp 115–116 °C; UV λ_{max} 303 nm (ϵ 1.02 × 10^4).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.14; H, 4.91; N, 18.61.

***N*-(β-Acetyloxy)ethyl-2-bromo-4-nitroaniline (13).** After 3.27 mL of 0.450 N tertiary-butanolic $KOC(CH_3)_3$ (0.00147 mol) had been added to a solution of 0.495 g (0.00147 mol) of **8** in 50 mL of Me_2SO, the mixture was stirred for 1 h at room temperature, poured into 100 mL of water, neutralized with hydrochloric acid (1 N), extracted with chloroform, and dried over anhydrous Na_2SO_4. After evaporation of the chloroform, recrystallization from ethanol gave **13** quantitatively (0.490 mg): mp 99.5–100.5 °C; UV λ_{max} 386 nm (ϵ 1.81 × 10^4).

Anal. Calcd for $C_{10}H_{11}BrN_2O_4$: C, 39.62; H, 3.66; N, 9.24. Found: C, 39.95; H, 3.71; N, 9.28.

***N*-(β-Hydroxy)ethyl-*N*-methyl-2-bromo-4-nitroaniline (14).** After 1.5 g (0.0204 mol) of *N*-methylethanolamine (NMEA) had been added to a solution of 1.5 g (0.0076 mol) of BNFB in 20 mL of dioxane, the mixture was stirred at room temperature for 20 h, poured into 50 mL of water, neutralized with aqueous HCl (1 N), extracted with chloroform, and dried over anhydrous Na_2SO_4. Chromatographic seperation (silica gel–benzene) followed by evaporation of the benzene gave 1.17 g of reddish light brown oil **14** (61%): UV λ_{max} 390 nm (ϵ 4.64 × 10^3). Several attempts to induce recrystallization failed.

Anal. Calcd for $C_9H_{11}BrN_2O_3$: C, 39.29; H, 4.03; N, 10.18. Found: C, 38.80; H, 4.31; N, 9.69.

***N*-(β-Hydroxy)ethyl-*N*-methyl-2-cyano-4-nitroaniline (19).** After 3.08 g (0.041 mol) of NMEA had been added to a solution of 3.0 g (0.0164 mol) of 6-chloro-3-nitrobenzonitrile (CNBN) in 50 mL of Me_2SO, the mixture was stirred for 10 h at room temperature, poured onto ice water, and extracted with chloroform, and recrystallization from ethanol gave 2.0 g (55%) of **19** (yellow crystals): mp 107–109 °C; UV λ_{max} 388 nm (ϵ 1.76 × 10^4).

Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.12; H, 5.12; N, 19.28.

***N*-(β-Acetyloxy)ethyl-2-cyano-4-nitroaniline (18).** After 2.5 g (0.0409 mol) of ethanolamine had been added to a solution of 3 g (0.0164 mol) of CNBN in 50 mL of Me_2SO, the mixture was stirred for 3 h at room temperature, poured into water, and neutralized with aqueous HCl (1 N). The raw product [*N*-(β-hydroxy)ethyl-2-cyano-4-nitroaniline, 2.0 g] was submitted to the following procedure without further purification. After 1.8 g (0.0229 mol) of acetyl chloride was added dropwise to a solution of 1.6 g of *N*-(β-hydroxy)ethyl-2-cyano-4-nitroaniline at room temperature, the mixture was stirred for 30 min at 60 °C, cooled, and poured onto ice water. The formed crude crystals were extracted with benzene, dried over anhydrous Na_2SO_4, and separated through a column (silica gel–benzene). Evaporation of the benzene and recrystallization from ethanol gave 1 g (51%) of **18** (brownish light-yellow crystals): mp 125–126 °C; UV λ_{max} 372 nm (ϵ 1.69 × 10^4).

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.90; H, 4.56; N, 16.90.

2-[*N*-(β-acetyloxy)ethyl]amino-5-nitropyridine (23). 5-Nitro-2-fluoropyridine was prepared according to the method described in the literature.[26] After 12.7 mL (0.00546 mol) of 0.430 N tertiary-butanolic $KOC(CH_3)_3$ was added dropwise to a solution of 1.23 g (0.00547 mol) of **10** in 50 mL of Me_2SO, the mixture was stirred 1 h, poured onto ice water, neutralized with aqueous HCl (1 N), extracted with chloroform, and dried over anhydrous Na_2SO_4. Evaporation of the chloroform and recrystallization from ethanol gave yellow crystals of **23** quantitatively: mp 124–125.5 °C; UV λ_{max} 369 nm (ϵ 1.77 × 10^4).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.10; H, 4.90; N, 18.57.

2-[*N*-(β-hydroxy)ethyl-*N*-methyl]amino-5-nitropyridine (24). After 1.18 g (0.0157 mol) of NMEA had been added to a solution of 1.0 g (0.00629 mol) of 5-nitro-2-chloropyridine, the mixture was stirred for 15 h at room temperature, poured onto ice water, extracted with chloroform, and dried over anhydrous Na_2SO_4. Evaporation of the chloroform and recrystallization from ethanol gave 0.80 g (65%) of **24** (yellow crystals): mp 88.5–90 °C; UV λ_{max} 387 nm (ϵ 2.03 × 10^4).

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.51; N, 5.38; N, 21.12.

Kinetic Data. Kinetic measurements for the rearrangement were made using a Hitachi-124 UV–vis spectrophotometer, except with **10**. Rate constants were calculated by monitoring the decrease in absorbance at 506 nm (λ_{max} of the spiro complex) with **5** or the increase in absorbance at 481, 475, and 462 nm with **8**, **9**, and **10**, respectively, at which wavelengths the reactants were transparent. In any given solvent, in which the Me_2SO content is always 96%, the ionic strength was kept at 0.1 ($KClO_4$). Runs were set up so that KOH as a base was in large excess over the substrate.

Kinetic measurements for the rearrangement of **10** and the formation of the anionic σ complexes from **8** and **10** were made by means of a Union RA-1200 rapid-reaction analyzer.

Preparation of Anionic σ Complexes for NMR Measurements. A certain amount of a sample (ca. 10^{-4}–10^{-5} mol) was dissolved in a small amount of Me_2SO (ca. 0.25 mL) in a NMR tube. After 1.0 or 1.5 equiv of tertiary-butanolic $KOC(CH_3)_3$ (ca. 0.4 N) had been added in the solution through a microsyringe and shaken vigorously, the mixture was submitted to measurement. The NMR data are summarized in Table III.[12]

Acknowledgment. We sincerely thank Mr. Katsuo Shinozaki for his partial contribution to the preparation of some compounds and Mr. Toshiaki Aizawa for the measurement of absorption spectra. The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education (1975 fiscal year).

Registry No.–**8**, 63989-43-5; **9**, 63989-50-4; **10**, 63989-49-1; **13**, 63989-48-0; **18**, 63989-47-9; **23**, 63989-46-8; **14**, 63989-45-7; **19**,

63989-44-6; **24**, 25948-15-6; **20**, 63988-97-6; **22**, 63988-99-8; **5**, 55759-61-0; **11**, 64011-18-3; **1**, 63989-41-3; **16**, 63988-98-7; **17**, 63989-42-4; NFB, 350-46-9; BNFB, 701-45-1; NAEA, 142-26-7; FNBN, 17417-09-3; 5-nitro-2-fluoropyridine, 456-24-6; NMEA, 109-83-1; CNBN, 16588-02-6; [*N*-(β-hydroxyethyl-2-cyano-4-nitroaniline, 63989-40-2; acetyl chloride, 75-36-5; 5-nitro-2-chloropyridine, 4548-45-2.

Supplementary Material Available. Table III and Figures 2, 5, 6, and 7 (6 pages). Ordering information is given on any current masthead page.

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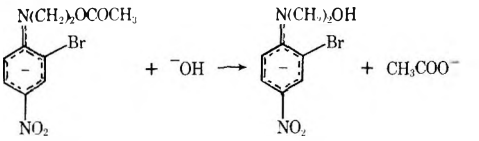

12 **12a**

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Crown–Cation Complex Effects. 8. Reactions of Crown Ether Activated *tert*-Butoxide Ion

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Received May 31, 1977

The effect of catalytic amounts of 18-crown-6 on tetrahydrofuran, *tert*-butyl alcohol, and benzene solutions of potassium *tert*-butoxide has been investigated. In each solvent, the enhanced nucleophilicity of *tert*-butoxide ion was manifested in its reaction with benzyl chloride; i.e., good yields of benzyl *tert*-butyl ether were obtained. In the latter solvent, 18-crown-6 served as phase-transfer agent as well as activator. *tert*-Butoxide ion was found to be most effective as a nucleophile in tetrahydrofuran solution, and, in general, the results of exemplary reactions indicated that nucleophilicity was enhanced more than basicity. Crown-activated *tert*-butoxide, for example, converts isatoic anhydride to *tert*-butyl anthranilate, benzaldehyde and diphenylmethane to benzhydryl phenyl ketone, and, in the presence of oxygen, fluorene directly to 2-carboxybiphenyl.

There has been interest for many years in solvent properties, particularly regarding their effect on the basicity and nucleophilicity of anionic reagents. The difference of 10^{11} in the rates of proton removal from carbon by alkoxide in methanol compared to dimethyl sulfoxide (Me_2SO) is an especially dramatic demonstration of such solvent effects.[1] Other studies conducted in the early 1960's demonstrated the value of *tert*-butoxide as a base, particularly in Me_2SO,[2,3] and it was at about this time that cation effects became clearly recognized.[4] A great deal is now known about the *tert*-butoxide ion[5] and, in general, about the chemistry of ion pairs.[6]

The ability of crown ethers to solvate cations has led to new studies of ion pairs both in the presence and absence of such ligands.[7] In general, in the presence of crown ether, aggregates of ion pairs are broken up and the anionic portion of the ligand separated or dissociated ion pair exhibits enhanced reactivity. This enhanced reactivity has manifested itself in decarboxylation reactions,[8] oxy-Cope rearrangements,[9] and elimination reactions.[10] We were particularly interested in the reactivity of potassium *tert*-butoxide (**1**) in the presence of crown ethers.[11] We felt that in such solvents as Me_2SO the enhanced basicity can be attributed, at least in part, to solvent assistance in carbanion formation.[12] In the presence of crown in a solvent such as tetrahydrofuran where solvent assistance is limited, the reactivity enhancement should be more apparent in the nucleophilic sense than in the basic sense. We have examined several reactions of *tert*-butoxide ion and have indeed found an enhancement of the nucleophilic behavior of this hindered base.

Results and Discussion

The chemistry of potassium *tert*-butoxide has been thoroughly reviewed.[5] This base has been utilized in a variety of media including *tert*-butyl alcohol, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, and benzene, although **1** is only sparingly soluble in the latter.[13] Benzyl chloride (**2**) has been used in the past as a substrate for studying nucleophile/base balance in systems where the anion behaved more as a base than as a nucleophile.[14] Utilization of this substrate

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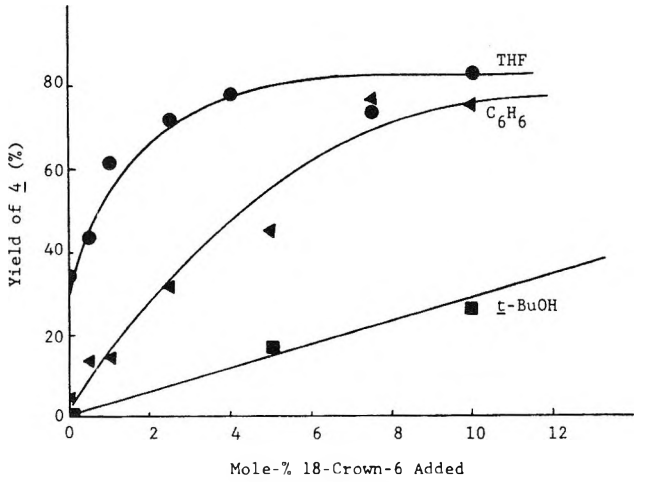


Figure 1. Yield of 4 as a function of added 18-crown-6.

for our purposes seemed particularly advantageous because the products of deprotonation are well known and the condensation product (benzyl *tert*-butyl ether) has always been accessible only with difficulty. Previous syntheses of benzyl *tert*-butyl ether required either long periods of time (e.g., 10 days at ambient temperature in *tert*-butyl alcohol to achieve a 55% yield)[15] or use of a dipolar aprotic solvent (30–40% yield after 18 h at ambient temperature in DMF).[16]

We have found that 1 readily condenses with 2 at 30 °C in tetrahydrofuran solution (see eq 1). In less than 2 h in the presence of 5 mol % 18-crown-6 (3),[17] benzyl *tert*-butyl ether (4) is isolated in 74% yield. The only by-product detected in this reaction is a small amount of stilbene (5). The stilbene apparently arises by deprotonation of 2, followed by nucleophilic substitution and then elimination of HCl. Although this sequence was not confirmed directly, the alternative of carbene dimerization was ruled out by conducting the reaction in a 1:1 mixture of cyclohexene and tetrahydrofuran (see Experimental Section). Any phenylcarbene generated should have been intercepted by the olefin to give 7-phenylnorcarane,[14a,b] none of which was detected (see eq 2).

$$\underset{1}{t\text{-}C_4H_9OK} + \underset{2}{C_6H_5CH_2Cl} \longrightarrow \underset{4}{t\text{-}BuOCH_2C_6H_5} + \underset{5}{C_6H_5CH{=}CHC_6H_5} \quad (1)$$

$$t\text{-}C_4H_9OK + 2 \xrightarrow{\text{/THF}} C_6H_5 \quad (2)$$

In order to determine whether the benzyl *tert*-butyl ether synthesis was solvent and/or crown concentration dependent, a series of experiments was conducted in which crown concentration was varied systematically in *tert*-butyl alcohol, benzene, and tetrahydrofuran (see Table I and Figure 1). In the latter solvent, the yields of 4 ranged from 34 to 83% when the reaction was conducted at 30 ± 1 °C for 1.0 h in the presence of 0.5–10 mol % 18-crown-6. As the amount of crown ether present was increased, the yield of ether increased as well, but the difference in yield between reactions containing 5 and 10 mol % added crown was negligible. The leveling of the yield curve is obvious in Figure 1. In the absence of any 18-crown-6, a 70% yield of 4 was realized, but only after 24 h. The amount of stilbene produced in each reaction was never more than 6% under any of the conditions utilized.

In contrast, the attempted synthesis of 4 in Me_2SO solution was unsuccessful, even less ether was produced than in the previously reported DMF case.[16] Apparently, 1 is much more basic in Me_2SO than in THF. Under conditions conducive to the formation of 4 (74% in 1 h at 30 °C) in THF, only 15% of this ether (4) could be detected. Although a small amount of 2 remained in the reaction mixture, stilbene was the major (47%) product. It seems very likely that crown or Me_2SO activated 1 is a potent anion, but, where the dipolar aprotic medium can offer solvent assistance in deprotonation, the basic behavior of the anion becomes dominant.

Table I

$$C_6H_5CH_2Cl^d + (CH_3)_3CO^-K^{+\,e} \xrightarrow[18C6]{THF} \underset{4}{C_6H_5CH_2OC(CH_3)_3}{}^f + \underset{5}{C_6H_5CH{=}CHC_6H_5}{}^g$$

Solvent	mol % added[b] crown ether[h]	Yield, %[c] 4	5
THF		34	0
THF	0.5	44	Trace
THF	1.0	62	5.0
THF	2.5	72	5.7
THF	5.0	78	4.4
THF	7.5	74	3.0
THF	10.0	83	1
C_6H_6		5	0
C_6H_6	0.5	14	0
C_6H_6	1.0	15	Trace
C_6H_6	2.5	32	~1
C_6H_6	5.0	45	2
C_6H_6	7.5	77	6.4
C_6H_6	10.0	75	8.6
t-C_4H_9OH		<1	0
t-C_4H_9OH	5.0	17	0
t-C_4H_9OH	10.0	26	0
t-C_4H_9OH	25.0	58	Trace

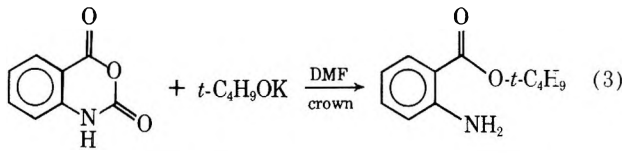
[a] All reactions were conducted at 30 ± 1 °C for 1 h under an atmosphere of N_2. [b] 18-crown-6; see ref 17. [c] Determined by GLC using a 5 ft × 0.25 in. 10% SE 30 column on NAW Chromosorb P, 60–80 mesh. [d] Registry no.: 100-44-7. [e] Registry no.: 865-47-4. [f] Registry no.: 3459-80-1. [g] Registry no.: 103-30-0. [h] Registry no.: 17455-13-9.

In *tert*-butyl alcohol, a solvent in which potassium *tert*-butoxide is also freely soluble,[13] the crown effect was also evident, although the yields of ether were lower even in the presence of considerably more crown and the yield increase as a function of added crown was nearly linear. Up to 25 mol % 18-crown-6 was added (see Table I and Figure 1) to the reaction mixture (under the conditions described above), and only 58% yield of ether was obtained. We feel that this reflects anion deactivation due to hydrogen bonding between the *tert*-butoxide ion and solvent. It is known that *tert*-butoxide is more basic (in elimination reactions) in the presence of crown than in its absence,[10] so it appears that both the nucleophilicity and basicity of this substance are enhanced by ion pair separation. The lesson seems to be that *tert*-butyl alcohol is not the best solvent for utilizing the potential of this synthetically important[5] reagent.

Potassium *tert*-butoxide is not profoundly soluble in benzene.[13b] This fact makes difficult a direct comparison of the reactivity of 1 in the presence and absence of 3. Nevertheless, in the synthesis of 4 according to eq 1, the yield per unit time of 4 was considerably increased in the presence of 3 (see Figure 1). It appears, in this particular case, that the crown serves as phase-transfer catalyst[18] as well as cation solvator and anion activator.[19]

The reaction of *tert*-butoxide with benzyl chloride to afford a high yield of 4 is, we believe, a convincing demonstration of the nucleophilicity of this ion in the presence of crown. Another such demonstration of this property can be found in the

reaction of *tert*-butoxide with isatoic anhydride. Although numerous anthranilate esters have been formed by nucleophilic addition of the appropriate alkoxide to isatoic anhydride (**6**),[20] it is reported that the *tert*-butyl ester cannot be formed by this approach.[21] In DMF solution, crown-activated *tert*-butoxide reacts with isatoic anhydride to afford *tert*-butyl anthranilate (**7**) in 33% yield (see eq 3). In the absence of crown this reaction is not preparatively useful (yield of **7** 8%).



(3)

The reactivity of *tert*-butoxide in THF is not enhanced sufficiently for this to afford a useful synthesis of phenyl *tert*-butyl ether from bromobenzene (see eq 4).[1,22] Since it appears that the nucleophilicity of *tert*-butoxide is enhanced more than is the basicity, the failure of eq 4, a reaction which apparently proceeds via a benzyne intermediate,[22] is not so surprising. On the other hand, the direct displacement of chloride by methoxide ion in 1,2-dichlorobenzene under crown catalysis[23] makes the necessity of the benzyne mechanism somewhat less certain.

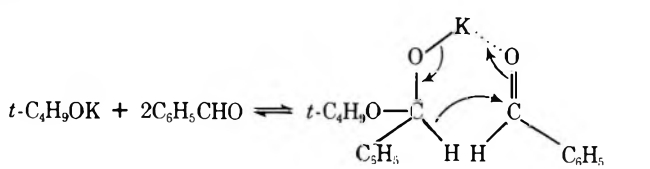
$$t\text{-}C_4H_9OK + C_6H_5Br \rightarrow t\text{-}C_4H_9OC_6H_5 \quad (4)$$

An approximate assessment of *tert*-butoxide ion's basicity under these conditions was obtained by equilibrating several carbon acids with crown-activated *tert*-butoxide ion in THF and then quenching with D_2O. Russell and co-workers showed some years ago that *tert*-butoxide in Me_2SO is basic enough to induce condensation between activated toluenes and benzaldehyde.[2] We have found that metallation of diphenylmethane (**8**) followed by a deuterium oxide quench gave a product which was 8% deuterated after 3 min and 18% deuterated after 4 h (recovery was ca. 90%). Chlorodiphenylmethane was 75% deuterated (by NMR) after only 30 s at 30 °C, although only 41% of the substrate could be recovered, the loss presumably due to ether formation in analogy to eq 1. No H–D exchange was observed for toluene even after 24 h at 30 °C.

Although metallation of **8** was not complete in 4 h, after 22 h in the presence of *tert*-butoxide it condensed with benzaldehyde to give α,α-diphenylacetophenone (**9**) according to eq 5. A more likely product in this reaction seemed to be triphenylethylene, but none was detected. An authentic sample of triphenylethylene survived the reaction conditions, implying that the product could not be accounted for by any process involving this substance as an intermediate.

$$C_6H_5CH_2C_6H_5 + C_6H_5CHO \rightarrow (C_6H_5)_2CHCOC_6H_5 \quad (5)$$

A possible mechanism is shown in eq 6. The sequence envisaged is addition of *tert*-butoxide ion to benzaldehyde to give an intermediate which then takes part in a Cannizzaro-like process to give *tert*-butyl benzoate. Diphenylmethyl anion is acylated by *tert*-butyl benzoate to give diphenylacetophenone in the final step of this reaction sequence. In favor of this mechanism is the fact that if **8** is excluded from the reaction mixture the products isolated are *tert*-butyl benzoate (29%) and benzyl alcohol (65%). We note that this reaction cannot occur by a single process strictly analogous to the Cannizzaro reaction because of the unequal product distribution. Moreover, **9** is produced in 15% yield from lithium diphenylmethide and *tert*-butyl benzoate in THF solution. Contrary to this mechanism, however, is the observation that, under the reaction conditions, diphenylmethane and *tert*-butyl benzoate do not produce detectable amounts of diphenylacetophenone.

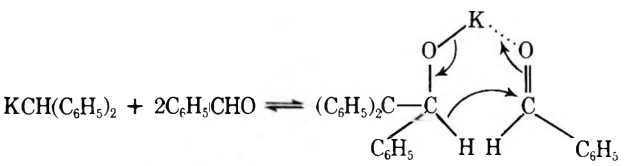


$$(C_6H_5)_2CH_2 + t\text{-}C_4H_9OK \rightleftharpoons (C_6H_5)_2CH^-K^+ + t\text{-}C_4H_9OH$$

$$(C_6H_5)_2CH^-K^+ + C_6H_5COO\text{-}t\text{-}C_4H_9 \rightarrow (C_6H_5)_2CHCOC_6H_5 + t\text{-BuOK} \quad (6)$$

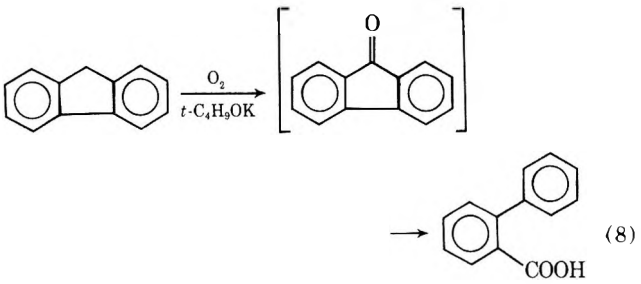
A possible mechanism which does not appear to be contradicted by any of our observations is shown in eq 7. Potassium *tert*-butoxide deprotonates diphenylmethane to give diphenylmethide ion which, in turn, adds to benzaldehyde. The resulting 1,2,2-triphenylethoxide ion then undergoes a Cannizzaro-type reaction as illustrated, resulting in formation of the observed ketone and benzyl alcohol. This second step must occur more rapidly than KOH can be lost because no triphenylethylene is detected in the reaction mixture (see above). When we conduct this reaction, we obtain 29% ketone and 35% alcohol, an approximately 1:1 distribution. When the reaction is carried out with benzaldehyde-α-*d*, ketone and alcohol are each isolated in 33% yield (slightly different workup) and the benzyl alcohol is, within the limits of detection, dideuterated at the methylene group. A kinetic investigation of this reaction would be interesting, but it is beyond the scope of this work.

$$KO\text{-}t\text{-}C_4H_9 + (C_6H_5)_2CH_2 \rightleftharpoons KCH(C_6H_5)_2 + HO\text{-}t\text{-}C_4H_9$$



$$\rightarrow (C_6H_5)_2CHCOC_6H_5 + C_6H_5CH_2OK \quad (7)$$

The crown-activated *tert*-butoxide reagent affords an interesting opportunity to carry out sequential reactions of the type mentioned above. For example, the basic oxidation of fluorene to fluorenone[25] in the presence of crown-activated *tert*-butoxide is rapid at room temperature (see eq 8). This



(8)

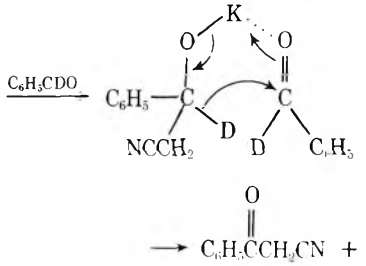
reaction occurs readily under phase-transfer conditions using cryptate-complexed hydroxide,[25a] 18-crown-6-complexed hydroxide,[25b] or quaternary ammonium hydroxides.[25c] A mole of water is produced in this reaction for each mole of hydrocarbon oxidized to ketone. Water is, in turn, deprotonated by excess *tert*-butoxide and Haller–Bauer cleavage[26] of the ketone ensues. In this way, fluorene can be transformed directly into 2-carboxybiphenyl in high yield according to eq 8. We note that in THF solution the crown effect is marginal. Our attempts to conduct this reaction with crown-activated hydroxide have thus far been unsuccessful.

The hoped-for condensation of acetonitrile with benzaldehyde to give cinnamonitrile[27] unadulterated by the β-hydroxynitrile (see eq 9) was less successful. In our particular attempts, the loss of yield was not due to the failure of the dehydration step, but rather due to a process analogous to that described in eq 7. Some cinnamonitrile is obtained in this reaction, but much of the benzaldehyde is lost to a Cannizzaro-type reaction. Specifically, when a THF solution of *tert*-butoxide, acetonitrile, and benzaldehyde-α-*d* was allowed to react, cinnamonitrile-β-*d* was isolated in 22% yield. Benzyl-d_2 alcohol was also isolated by preparative GLC from this same reaction mixture. The conclusion we draw from these observations is that cyanomethyl anion adds to benzaldehyde to give the β-alkoxynitrile. This alkoxynitrile can either lose KOH (or protonate and lose water) or it can undergo a Cannizzaro-type reaction as shown in eq 10. The cyanoacetophenone produced in this reaction is quite acidic and undoubtedly undergoes multiple condensations with benzaldehyde and *tert*-butoxide.

$$C_6H_5CHO + CH_3CN \xrightarrow[\text{crown}]{t\text{-}C_4H_9OK} C_6H_5CH{=}CHCN + C_6H_5CHOHCH_2CN \quad (9)$$

$$t\text{-}C_4H_9OK + CH_3CN \rightleftharpoons t\text{-}C_4H_9OH + KCH_2CN$$

$$KCH_2CN + C_6H_5CDO \rightleftharpoons C_6H_5CDCH_2CN$$



$$\rightarrow C_6H_5CCH_2CN + C_6H_5CD_2OK \quad (10)$$

We note that the condensation of acetonitrile with benzaldehyde to afford cinnamonitrile has been achieved under other conditions which we have reported previously.[28]

Summary. In summary, it appears that potassium *tert*-butoxide in THF in the presence of crown ether is both a powerful nucleophile and base, but the enhancement of nucleophilicity appears to exceed the enhancement of the basicity. The reagent is a potent nucleophile giving hitherto unattainable yields in several exemplary reactions. The system is of value because it appears to compliment the Me_2SO enhanced basicity of *tert*-butoxide. Moreover, the fact that only a catalytic amount of crown appears necessary to observe the enhanced reactivity is of practical value in synthetic applications.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary device and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 and are calibrated against the 1601 cm^{-1} band of polystyrene. NMR spectra were recorded on a Varian Associates A-60A as ca. 15 wt % solutions in CCl_4 or $CDCl_3$. Chemical shifts are reported in ppm (δ) downfield from internal Me_4Si. Mass spectra were determined on an AEI-MS 902 instrument at an ionizing voltage of 70 eV. Gas chromatographic analyses were conducted using either a Varian Associates Model 2720 or 920 analytical gas chromatograph equipped with a thermal-conductivity detector and a 5 ft × 0.25 in. 10% SE-30 column on NAW Chromosorb P. Helium was used as a carrier gas and the flow rate was ca. 60 mL/min.

Tetrahydrofuran was distilled from $LiAlH_4$ through a 30-cm Vigreux column just prior to use. The potassium *tert*-butoxide was sublimed and stored thereafter under dry nitrogen in a desiccator. All other solvents were purified according to literature procedures and stored under dry nitrogen and in contact with 4-Å molecular sieves.

Preparation of Benzyl *tert*-Butyl Ether (in Tetrahydrofuran). A 100-mL, three-necked, round-bottomed flask equipped with an addition funnel and magnetic stirring bar was charged with resublimed potassium *tert*-butoxide (5.61 g, 0.05 mol), 18-crown-6 (0.66 g, 0.0025 mol), and dry THF (40 mL). The solution was placed in a 30 °C bath and the solution was maintained under an inert atmosphere (N_2). Benzyl chloride (6.32 g, 0.05 mol) in THF (10 mL) was added dropwise over 5 min. After the addition was complete, stirring was continued for 1 h, the mixture was quenched with water (5 mL), diluted with an equal volume of ether and filtered, and the filtrate was dried over sodium sulfate and evaporated in vacuo. Benzyl *tert*-butyl ether (6.1 g, 74%) was obtained after distillation (bp 90–92 °C/15 mm) as a colorless oil: NMR (CCl_4, ppm) 1.2 (ψs, 9 H) $-C(CH_3)_3$, 4.3 (ψs, 2 H) $ArCH_2$, 7.2 (ψs, 5 H) aromatic protons. Recrystallization of the pot residue from ethanol/benzene gave (*E*)-stilbene as an off-white solid: 220 mg; 5%; mp 120–121 °C; NMR ($CDCl_3$, ppm) 7.0 (ψs, 2 H) ArCH=CHAr, 7.1–7.5 (m, 10 H) aromatic protons.

Reaction of Benzyl Chloride with Crown-Activated Potassium *tert*-Butoxide in 1:1 THF/Cyclohexene. A 50-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and nitrogen inlet was charged with THF (5 mL), cyclohexene (10 mL), potassium *tert*-butoxide (1.12 g, 0.01 mol), and 18-crown-6 (0.132 g, 0.0005 mol). The solution was brought to 30 °C and a solution of benzyl chloride (1.26 g, 0.01 mol) in THF (5 mL) was added dropwise over a period of 5 min. After the addition was complete, stirring was continued for 1 h, the mixture was quenched with water (5 mL) and separated, and the organic phase was washed with water (20 mL). The aqueous phase was extracted with ether (20 mL), and the combined organic phase was dried over sodium sulfate and analyzed (GLC) to show benzyl *tert*-butyl ether (93%), stilbene (~1%), and a small amount of unreacted benzyl chloride. No 7-phenylnorcarane could be detected.

Reaction of Benzyl Chloride with Potassium *tert*-Butoxide in Me_2SO. A 100-mL, three-necked, round-bottomed flask equipped with an addition funnel and magnetic stirring bar was charged with potassium *tert*-butoxide (1.12 g, 0.01 mol) and dry Me_2SO (15 mL). The solution was brought to 30 °C under a nitrogen atmosphere and a solution of benzyl chloride (1.26 g, 0.01 mol) in Me_2SO (5 mL) was added dropwise over a period of 5 min. After the addition was complete, stirring was continued for 1 h, and the mixture was quenched with water (5 mL) and diluted with an equal volume of ether. The resulting mixture was washed with water (3 × 20 mL) and the aqueous phase backwashed with ether (20 mL). The combined organic phase was dried over sodium sulfate and analyzed by GLC (see above). Stilbene (47%), benzyl *tert*-butyl ether (15%), and a small amount of unreacted benzyl chloride were detected.

Reaction of Benzyl Chloride with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. A 100-mL, three-necked, round-bottomed flask equipped with an addition funnel and magnetic stirring bar was charged with potassium *tert*-butoxide (1.12 g, 0.01 mol), 18-crown-6 (0.66 g, 0.0025 mol), and dry *tert*-butyl alcohol (15 mL). The solution was brought to 30 °C under a nitrogen atmosphere and a solution of benzyl chloride (1.26 g, 0.01 mol) in *tert*-butyl alcohol (5 mL) was added dropwise over a period of 5 min. After the addition was complete, stirring was continued for 1 h, and the mixture was quenched with water (5 mL), diluted with an equal volume of ether, and filtered. The filtrate was dried over sodium sulfate and analyzed by GLC (see above). Benzyl *tert*-butyl ether (58%), unreacted benzyl chloride (28%), and stilbene (<1%) were detected.

Preparation of *tert*-Butyl Anthranilate. A 250-mL, three-necked, round-bottomed flask equipped with addition funnel, nitrogen inlet, and magnetic stirring bar was charged with isatoic anhydride (8.2 g, 0.05 mol) and dry DMF (50 mL). After the anhydride had dissolved, a solution of potassium *tert*-butoxide (6.1 g, 0.051 mol) and 18-crown-6 (0.66 g, 0.0025 mol) in DMF (25 mL) was added dropwise. The dark solution was stirred for 24 h, quenched with distilled water (100 mL), and extracted with ether (4 × 100 mL). The combined organic material was washed with distilled water (100 mL) and brine (100 mL), dried over sodium sulfate, and evaporated in vacuo. After distillation (bp 82–90 °C/0.35–0.45 mm), *tert*-butyl anthranilate was obtained (3.12 g, 33%) as a pale-yellow oil: NMR (CCl_4, ppm) 1.56 (s, 9 H) $-C(CH_3)_3$, 6.6 (m, 2 H) $-NH_2$, 6.45 (m, 2 H), 7.0 (m, 1 H), 7.6 (m, 1 H) aromatic protons; IR (neat) $\nu_{C=O}$ 1690 cm^{-1}. High-resolution mass spectrum, calcd: 193.1099; found: 193.1102. (NB: An identical reaction in the absence of 18-crown-6 produced *tert*-butyl anthranilate in only 8% yield.)

Attempted Synthesis of Phenyl *tert*-Butyl Ether. A 200-mL

pressure reaction bottle equipped with a magnetic stirring bar was charged with potassium *tert*-butoxide (2.80 g, 0.025 mol), 18-crown-6 (0.33 g, 0.00125 mol), bromobenzene (3.9 g, 0.025 mol), and THF (50 mL). The contents were then sealed under a nitrogen atmosphere, immersed in a 100 °C oil bath, and stirred for 2 h. The reaction mixture was then allowed to cool to room temperature, quenched with water (2 mL), diluted with ether (10 mL), and filtered. The filtrate was reduced in vacuo to give a brown oil from which all volatile material was distilled (bp 45–50 °C, ~15 mm). The distillate was analyzed by NMR and found to consist largely of unreacted bromobenzene with a small amount of phenyl *tert*-butyl ether (NMR).

Metallation of Diphenylmethane with *tert*-Butoxide. A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with THF (40 mL), potassium *tert*-butoxide (2.80 g, 0.025 mol), and 18-crown-6 (0.33 g, 0.00125 mol), and then immersed in a bath maintained at 30 °C. Diphenylmethane (4.1 g, 0.025 mol) in THF (10 mL) was added dropwise, and the solution was stirred for 4 h, quenched with D_2O (2 mL), and diluted with ether (20 mL). The precipitated salts were removed by filtration and the filtrate was reduced in vacuo to a pale-yellow oil. After distillation (bp 132 °C, ~10 mm), diphenylmethane, 18% deuterated (NMR integration), was obtained as a colorless oil (3.6 g, 87% recovery): NMR (CCl_4, ppm) 3.88 (s, 1.64 H) $(Ar)_2CHd$, 7.08 (s, 5 H) aromatic protons.

Metallation of Chlorodiphenylmethane with *tert*-Butoxide. Chlorodiphenylmethane was added in a stream and metallated as above for 30 s, and D_2O (2 mL) was then added. After distillation (bp 164–165 °C, ~20 mm) chlorodiphenylmethane [75% deuterated at C-1 (NMR integration)] was obtained as a colorless oil (41% recovery): NMR (CCl_4, ppm) 5.95 (ψs, 0.25 H) $(Ar)_2ClCH(D)$, 7.18 (m, 10 H) aromatic protons.

Attempted Metallation of Toluene with Crown-Activated *tert*-Butoxide. A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with THF (40 mL), potassium *tert*-butoxide (2.80 g, 0.025 mol), and 18-crown-6 (0.33 g, 0.00125 mol), and then immersed in a bath maintained at 30 °C. Toluene (2.30 g, 0.025 mol) in THF (10 mL) was added dropwise, and the solution was stirred for 24 h, quenched with D_2O (2 mL), and diluted with ether (20 mL). The precipitated salts were removed by filtration and the filtrate was reduced in vacuo (bath temp ca. 35 °C) to a pale-yellow oil. Analysis of the crude recovered toluene (NMR integration) indicated no deuteration.

***tert*-Butoxide-Catalyzed Reaction of Diphenylmethane with Benzaldehyde.** A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet and maintained at 30 °C was charged with THF (40 mL), potassium *tert*-butoxide (2.80 g, 0.025 mol), and 18-crown-6 (0.33 g, 0.00125 mol). Diphenylmethane (4.10 g, 0.025 mol) in THF (5 mL) was then added in a stream. After allowing 30 min for metallation, benzaldehyde (2.65 g, 0.025 mol) in THF (5 mL) was added dropwise, and the resulting mixture was stirred overnight (22 h). The α,α-diphenylacetophenone which precipitated upon addition of water (100 mL) was collected by filtration and the residue crystallized from hexane. The ketone was obtained (2.0 g, 29% based on diphenylmethane) as a white solid: mp 134–135 °C; lit.[29] mp 136 °C, mmp 132 °C; NMR ($CDCl_3$, ppm δ) 6.03 (ψs, 1 H) $ArCOCHAr_2$, 7.28 (ψs, 11 H), 7.45 (ψd, 2 H), 8.0 (m, 2 H) aromatic protons; IR (mull) $\nu_{C=O}$ 1685 cm^{-1}.

The aqueous phase was extracted with ether which was then dried (Na_2SO_4) and reduced in vacuo to a pale-yellow oil. Column chromatography (80–325 mesh alumina) using 2% ether–hexane as solvent gave diphenylmethane (1.73 g, 42%). Elution with 1:1 (v/v) ether/hexane gave benzyl alcohol (0.97 g, 35%). (NB: No *tert*-butyl benzoate was detected in this experiment.)

Reaction of Benzaldehyde with Crown-Activated Potassium *tert*-Butoxide. A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet and maintained at 30 °C was charged with THF (40 mL), potassium *tert*-butoxide (2.80 g, 0.025 mol), and 18-crown-6 (0.330 g, 0.00125 mol). A solution of benzaldehyde (2.65 g, 0.025 mol) in THF (10 mL) was added dropwise, and the resulting highly colored mixture was stirred for 2 h, quenched with water (2 mL), diluted with ether (20 mL), and filtered. The filtrate was dried over sodium sulfate and reduced in vacuo to a pale-yellow oil. Purification by column chromatography as above gave benzyl alcohol (1.87 g, 65%) and *tert*-butyl benzoate (1.28 g, 29%): NMR (CCl_4, ppm) 1.58 (s, 9 H) $-C(CH_3)_3$, 7.4 (m, 3H), 7.95 (m, 2 H) aromatic protons; IR (neat): $\nu_{C=O}$ 1710 cm^{-1}.

Acylation of Lithium Diphenylmethide by *tert*-Butyl Benzoate. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, serum cap, addition funnel and nitrogen inlet was charged with THF (40 mL) and diphenylmethane (1.68 g, 0.01 mol). The solution was cooled to 0 °C and 2.4 M *n*-butyllithium (4.16 mL, 0.01 mol) was syringed in, and the solution was stirred for 30 min. *tert*-Butyl benzoate (1.78 g, 0.01 mol) in THF (10 mL) was then added dropwise, and the solution was stirred for 1 h, quenched, and diluted with water (5 and 100 mL, respectively). The α,α-diphenylacetophenone which precipitated was collected by filtration and the residue crystallized from hexane. The ketone was obtained (0.41 g, 15%) as a white solid, mp 134–135 °C.

Reaction of Diphenylmethane with Benzaldehyde-*d*. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, and addition funnel was charged with THF (15 mL), potassium *tert*-butoxide (1.12 g, 0.01 mol) and 18-crown-6 (0.132 g, 0.0005 mol). Diphenylmethane (1.68 g, 0.01 mol) was syringed in. After allowing 30 min for metallation, benzaldehyde-*d* (1.07 g, 0.01 mol) in THF (5 mL) was added dropwise, and the resulting mixture stirred overnight (22 h) and then quenched with water (5 mL). The mixture was diluted with water (50 mL) and extracted with ether (3 × 25 mL), and the combined organic phases were dried over sodium sulfate. Column chromatography (80–325 mesh alumina, hexane solvent) gave diphenylmethane (1.01 g, 60%). Elution with 5% ether–hexane gave α,α-diphenylacetophenone (0.86 g, 33% based on diphenylmethane), mp 130–132 °C, mmp 133–134 °C, containing no deuterium (NMR). Further elution with 1:1 (v/v) ether–hexane gave benzyl-α,α-d_2 alcohol (0.36 g, 33% based on diphenylmethane) identified by NMR.

Attempted *tert*-Butoxide-Catalyzed Acylation of Diphenylmethane with *tert*-Butyl Benzoate. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and nitrogen inlet was charged with potassium *tert*-butoxide (1.12 g, 0.01 mol), 18-crown-6 (0.132 g, 0.0005 mol), and dry THF (40 mL). The solution was brought to 30 °C under a nitrogen atmosphere and a solution of diphenylmethane (1.64 g, 0.01 mol) in THF (5 mL) was added dropwise and allowed to react for 10 min. A solution of *tert*-butyl benzoate (1.78 g, 0.01 mol) in THF (5 mL) was then added dropwise over a period of 5 min. After the addition was complete, stirring was continued for 24 h, and the mixture was quenched and diluted with water (5 and 10 mL, respectively). Any α,α-diphenylacetophenone present failed to precipitate after 24 h. The resulting oil was extracted with dichloromethane (2 × 25 mL), dried over sodium sulfate, filtered, and reduced in vacuo to a brown oil. No α,α-diphenylacetophenone could be detected by NMR (benzhydryl proton at δ 6.03), although unreacted diphenylmethane and *tert*-butyl benzoate were readily detected. The same result was obtained when the reaction was conducted for 48 h.

Preparation of 2-Carboxybiphenyl. A 100-mL, round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and gas inlet was charged with potassium *tert*-butoxide (2.24 g, 0.02 mol), 18-crown-6 (0.066 g, 0.00025 mol), and THF (40 mL). The solution was placed under an atmosphere of oxygen and a solution of fluorene (0.83 g, 0.005 mol) in THF (10 mL) was added over a period of 5 min. After the addition was complete, stirring was continued under oxygen for 1 h. Then, the reaction was quenched with water (10 mL) and the aqueous phase separated. The organic phase was washed with water (2 × 25 mL) and the combined aqueous phase acidified with concentrated HCl. The acid was then extracted with ether (3 × 20 mL), dried over sodium sulfate, and evaporated in vacuo. There was obtained 2-carboxybiphenyl (0.99 g, 100%) as a yellow solid: mp 109–110 °C; lit.[30] mp 112–112.5 °C; NMR ($CDCl_3$, ppm) 7.23 (ψs, 8 H), 7.72 (m, 1 H) aromatic protons, 11.5 (m, 1 H) –COOH; IR (mull): $\nu_{C=O}$ 1685 cm^{-1}. (NB: An identical reaction in the absence of 18-crown-6 produced 2-carboxybiphenyl in 92% yield.)

Potassium *tert*-Butoxide/Crown Catalyzed Condensation of Benzaldehyde-*d* with Acetonitrile. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and nitrogen inlet was charged with potassium *tert*-butoxide (1.12 g, 0.01 mol), 18-crown-6 (0.132 g, 0.0005 mol), and THF (15 mL). The solution was stirred at ambient temperature (ca. 27 °C) and acetonitrile (0.41 g, 0.01 mol) was added in one portion. After allowing 10 min for metallation, a solution of benzaldehyde-*d* (1.07 g, 0.01 mol) in THF (5 mL) was added dropwise over a period of 5 min. After the addition was complete, stirring was continued for 3 h, and the mixture was quenched with water (5 mL), diluted with ether (25 mL), and washed with water (3 × 25 mL). The combined aqueous phase was backwashed with ether (25 mL) and the organic phase dried over sodium sulfate. Column chromatography (80–325 mesh alumina) using 1:9 (v/v) ether–hexane as solvent gave cinnamonitrile-β-*d* (0.25 g, 22% *E*/*Z* ~7.1) as a pale-yellow oil: NMR (CCl_4, ppm) *E* isomer, 5.71 (ψt, 1 H) ArCD=CHCN, 7.3 (ψs, 5 H) aromatic protons; *Z* isomer, 5.31 (m, 1 H) ArCD=CHCN, 7.3 (ψs, 5 H) aromatic protons; IR (neat): $\nu_{C\equiv N}$ 2220 cm^{-1}, elution with 3:7 (v/v) ether–hexane followed by

preparative GLC (gas chromatography gave benzyl-α,α-d_2 alcohol identified by NMR).

Acknowledgment. We warmly thank Organic Reactions, Inc., and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for grants which supported this work.

Registry No.—Isatoic anhydride, 118-48-9; *tert*-butyl anthranilate, 64113-91-3; diphenylmethane, 101-81-5; deuterated diphenylmethane, 20389-18-8; α,α-diphenylacetophenone, 1733-63-7; benzaldehyde, 100-52-7; *tert*-butyl benzoate, 774-65-2; benzaldehyde-*d*, 3592-47-0; benzyl-α,α-d_2 alcohol, 21175-64-4; 2-carboxybiphenyl, 947-84-2; fluorene, 86-73-7; acetonitrile, 75-05-8; (*E*)-cinnamonitrile-β-*d*, 64113-90-2; (*Z*)-cinnamonitrile-β-*d*, 64113-89-9; deuterated chlorodiphenylmethane, 778-23-40.

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Base-Catalyzed β-Elimination Reactions. 7. Elimination from 4-(Para-substituted-phenoxy)-2-oxobutanoic Acids

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Received August 22, 1977

Elimination of para-substituted phenoxides from 4-(para-substituted-phenoxy)-2-oxobutanoic acids in aqueous solution is catalyzed by imidazole, morpholine, diethanolamine, and *N,N*-dimethylethanolamine. The dependence of the pseudo-first-order rate constant on amine concentration is nonlinear, with an initial line of large slope at low amine concentration which changes to a line of smaller slope at high amine concentration. The existence of a carbanion intermediate in the reaction is supported by the result that α-hydrogen exchange at high amine concentration is faster than elimination. These findings, coupled with the results of analysis of Hammett ρ' values for various steps of the elimination reaction catalyzed by morpholine, lead us to conclude that elimination proceeds via spontaneous decomposition of enolates and general-base-catalyzed decomposition of enols.

A considerable body of evidence indicates that many base-catalyzed β-elimination reactions proceed via carbanion intermediates.[1-6] For example, under the experimental conditions employed, β-elimination of para-substituted phenoxides from 4-(para-substituted-phenoxy)-2-butanones is adequately described by the minimal mechanism of Scheme I.[5]

Many biochemical reactions such as aldolization,[7-9] decarboxylation,[10] carboxylation,[8] and elimination[11-13] are thought to occur via proton transfer to form a carbanion intermediate from α-keto acid substrates, and our own interest in carbanion chemistry is related in part to our desire to understand enzyme catalysis. In order to better understand the chemistry of elimination reactions, specifically in compounds capable of stabilizing enols, and to develop potential suicide substrates[14-16] for those enzymes which utilize α-keto acid

Scheme I

$$\mathrm{ArOCH_2CH_2COCH_3} \underset{k_2,\ \mathrm{BH}}{\overset{k_1,\ \mathrm{B}}{\rightleftharpoons}} \mathrm{ArOCH_2CHCOCH_3^-} \xrightarrow{k_3} \mathrm{CH_2{=}CHCOCH_3} + \mathrm{ArO^-}$$

0022-3263/78/1943-0452$01.00/0

substrates, we synthesized four 4-(para-substituted-phenoxy)-2-oxobutanoic acids (X = H (1), CH_3 (2), CH_3O (3), and Cl (4)) and studied their base-catalyzed elimination reactions (eq 1). This study showed that β-elimination reactions are facile, that elimination occurs via general-base-catalyzed proton transfer to form carbanions, and that the reaction is necessarily more complex than the simple E1cB reaction mechanism of Scheme I.

$$p\text{-X-C}_6\text{H}_4\text{OCH}_2\text{CH}_2\text{COCO}_2^- \rightarrow p\text{-X-C}_6\text{H}_4\text{OH} + \text{CH}_2{=}\text{CHCOCO}_2^- \quad (1)$$

Experimental Section

Apparatus. The apparatus used for collection of rate data was previously described.[5] Calculations were performed on either a Hewlett Packard 2700 calculator using the first-order kinetics data and linear regression programs from the program library provided or on a Hewlett Packard HP 25 calculator. The plots of the pseudo-first-order rate constants vs. concentration of base were fitted to curves by the CDC 6400 computer of the State University of New York at Buffalo, using the NLIN 2 curve-fitting program from the program library of the State University of New York at Buffalo. NMR spectra were taken on either Varian A-60 or T-60 instruments with Me_4Si as an internal standard, and the proton signals are reported in δ values downfield from Me_4Si. Melting points were taken in open capillary tubes in a Mel-Temp apparatus and are uncorrected.

Reagents. All inorganic reagents were Fisher Certified ACS Grade, except D_2O (99.8% D), Stohler Isotope Chemicals, DCl (+99% D), and KOD (98% D), Aldrich Chemical Co. All organic reagents were purchased from Aldrich Chemical Co. Tap-distilled water was redistilled through a Corning aGla still before use.

Kinetics. All reactions were carried out at 30 ± 0.1 °C in aqueous solution and at an ionic strength of 1.0 M maintained with KCl. The pH of solutions was measured and found to be constant, ±0.02 pH unit, for all serial dilutions of constant catalytic buffer ratio. In addition, the pH of reaction solutions was taken after each run, and the pH change never exceeded 0.08 pH unit; pH drift occurred in the very dilute buffers. Reactions were run under pseudo-first-order conditions with substrate concentration ~2×10^{-4} M. The reactions were initiated by addition of the substrate in ethanol to amine or hydroxide solutions, except in cases where the reaction proved to be too fast to monitor by these conditions. For reactions which had pseudo-first-order rate constants greater than ~8.5 min^{-1}, 3 mL of the amine or hydroxide solution, which had been equilibrated at a temperature of 30 °C in a constant-temperature bath, was rapidly added to a cuvette containing the substrate using an Oxford macro-transfer pipet. Reactions were monitored by following the appearance of phenol or phenoxide, depending on the pH, at the following wavelengths (compound, phenol, phenoxide): 4-phenoxy-2-oxobutanoic acid (1), 278, 286 nm; 4-(*p*-cresoxy)-2-oxobutanoic acid (2), 286, 296 nm; 4-(*p*-anisoxy)-2-oxobutanoic acid (3), 304, 309 nm; 4-(*p*-chlorophenoxy)-2-oxobutanoic acid (4), 294, 310 nm.

Products. The course of the reaction of each of the compounds 1–4 with 0.04 M KOH was scanned from 210 to 410 nm. In each case, the appearance of para-substituted phenoxides was confirmed by spectral comparisons using authentic para-substituted phenols. Relatively strong absorption of phenoxides coupled with the presumed instability of 2-oxobutenoic acid[2] prevented detection of this acid by UV spectroscopy. Reaction of 4-(*p*-chlorophenyl)-2-oxobutanoic acid with 0.04 M KOD in D_2O was monitored by NMR spectrometry. The reaction product showed an absorption at δ 6.38 which we attribute to vinyl protons in an α,β-unsaturated carbonyl system. A signal at δ 6.38 was found for the unstable pyrolysis products of 4-*N*,*N*-diethylamino-2-oxobutanoic acid.[17] The amount of *p*-cresoxide ion formed on reaction of 2.5×10^{-4} M **2** in 0.04 M KOH was quantitated. After reaction, the concentration of *p*-cresoxide ion was 2.58×10^{-4} M, calculated from the absorbance (0.703) at 296 nm and the molar extinction coefficient 2.73×10^3 M^{-1} cm^{-1}, which was obtained from the data of Lang.[18]

Syntheses. Diethoxyacetic acid, bp 81 °C (0.3 mm), was prepared in 83% yield by the method of Moffett.[19]

Benzyl Diethoxyacetate. A solution of saturated aqueous K_2CO_3 was added dropwise to 22.5 g (0.15 mol) of diethoxyacetic acid until no more CO_2 was evolved, and the pH was between 7.5 and 8. The water was then evaporated in a rotary evaporator, and the carboxylate salt was added to 28.9 g (0.228 mol) of benzyl chloride in 300 mL of dimethylformamide. The mixture was heated to 90 °C with stirring for 1 h. Benzene was added to the cooled mixture which was then washed with three portions of water. The organic solution was collected and dried ($MgSO_4$), and benzene and DMF were removed on a rotary evaporator. Distillation gave a forerun of benzyl chloride followed by benzyl diethoxyacetate: yield 37.5 g (76%); bp 99–101 °C (0.05 mm); NMR ($CDCl_3$) 1.22 (t, 6 H), 3.64 (q, 4 H), 4.91 (s, 1 H), 5.19 (s, 2 H), 7.31 (s, 5 H).

2-Carbobenzoxy-1,3-dithiane. The method of Eliel[20] was used. A solution of 4.6 g (42.4 mmol) of 1,3-propanedithiol and 13.6 g (57.1 mmol) of benzyl diethoxyacetate in 50 mL of $CHCl_3$ was added dropwise to a refluxing solution of 12 g (85.2 mmol) of boron trifluoride etherate in 100 mL of $CHCl_3$. The solution was refluxed for 0.5 h, cooled, and washed with 80 mL of H_2O, 80 mL of 10% aqueous K_2CO_3, and then with two 80-mL portions of H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and $CHCl_3$ removed in a rotary evaporator, leaving crystals which were recrystallized twice from hexane: yield 9 g (62%); mp 72–75 °C; NMR ($CDCl_3$) 1.79–2.32 (m, 2 H), 2.47 (t, 1 H), 2.55 (t, 1 H), 3.41 (m, 2 H), 4.25 (s, 1 H), 5.25 (s, 2 H), 7.41 (s, 5 H).

2-(β-Para-substituted-phenoxy)ethyl-2-carbobenzoxy-1,3-dithianes. Para-substituted bromophenetoles, with the exception of β-bromophenetole (Aldrich Chemical Co.), were prepared by the method of Adams and Thol[21] (compound, mp, yield): *p*-CH_3, 48–50 °C, 38%; *p*-CH_3O, 49–50 °C, 51%; *p*-Cl, 40–41 °C, 32%. The following general method was employed using 10–60 mmol quantities of the β-bromophenetole. a solution of 2-carbobenzoxy-1,3-dithiane in DMF/benzene (3:1) was added dropwise to a stirred suspension of an equimolar quantity of NaH in 150 mL of DMF/benzene (3:1) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then a 1.2 mol excess of the desired para-substituted β-bromophenetole in a solution of DMF/benzene (3:1) was added dropwise with stirring. The temperature of the mixture was allowed to rise to 25 °C, and the mixture was stirred for 15 h at 25 °C. Benzene was then added to the mixture, and the organic layer was washed three times with water. The solvent was removed by rotary evaporation, and the product was crystallized and recrystallized from hexane. Melting points and yields are as follows: *p*-H, 55–58 °C, 43%; *p*-CH_3, 50–53 °C, 55%; *p*-CH_3O, 63–64 °C, 59%; *p*-Cl, 55–56 °C, 59%. NMR ($CDCl_3$): *p*-H 1.87 (t, 2 H), 2.56 (m, 4 H), 2.86–3.53 (dtd, 2 H). 4.16 (t, 2 H), 5.16 (s, 2 H), 6.46–7.23 (m, 5 H), 7.26 (s, 5 H); *p*-CH_3 2.02 (m, 2 H), 2.35 (s, 3 H), 2.67 (m. 2 H), 3.14–3.66 (dtd, 2 H), 4.3 (t, 2 H), 5.41 (s, 2 H), 6.85–7.4 (dd, 4 H), 7.6 (s, 5 H); *p*-CH_3O 1.89 (m, 2 H), 2.55 (m, 4 H), 2.96–3.54 (dtd, 2 H), 3.72 (s, 3 H), 4.15 (t, 2 H), 5.21 (s, 2 H), 6.76 (s, 4 H), 7.34 (s, 5 H); *p*-Cl 1.87 (m, 2 H), 2.6 (m, 4 H), 2.9–3.7 (dtd, 2 H), 4.12 (t, 2 H), 5.2 (s, 2 H), 6.73 (d, 2 H), 7.15 (d, 2 H), 7.31 (s, 5 H).

Benzyl 4-(Para-substituted-phenoxy)-2-oxobutanoates. Very specific conditions, similar to those of Corey and Erickson,[22] were employed. 2-(β-Para-substituted-phenoxy)ethyl-2-carbobenzoxy-1,3-dithiane (20 mmol) in 5 mL of an acetone solution was added dropwise to a stirred suspension of *N*-chlorosuccinimide and silver nitrate (1:4:4.5 mol ratio). The addition was made as rapidly as possible while maintaining the reaction temperature at 25 °C by the use of an ice bath. After the addition, the mixture was stirred for 5 min at 25 °C; longer times tended to give lower yields. The reaction was stopped by cooling the reaction mixture to 0 °C and then adding, at 1-min intervals, 5 mL each of saturated $NaHSO_3$, 10% $NaHCO_3$, H_2O, and saturated NaCl. Hexane/CH_2Cl_2 (1:1) was added, and the mixture was filtered through Celite. The organic phase was separated and dried ($MgSO_4$), and the solvent was flash-evaporated to give benzyl 4-(para-substituted-phenoxy)-2-oxobutanoates, which were crystallized and recrystallized from hexane/CS_2 (9:1). Melting points and yields are as follows: *p*-H, 49.5–51 °C, 22%; *p*-CH_3, 66–67 °C, 26%; *p*-CH_3O, 45–45°C, 11%; *p*-Cl, 82.5–84.5 °C, 34%. NMR: *p*-H 3.33 (t, 2 H), 4.37 (t, 2 H), 5.43 (s, 2 H), 6.88–7.55 (m, 5 H), 7.6 (s, 5 H); *p*-CH_3 2.33 (s, 3 H), 3.32 (t. 2 H), 4.33 (t, 2 H), 5.36 (s, 2 H), 6.75–7.3 (q, 4 H), 7.47 (s, 5 H); *p*-CH_3O 3.18 (t, 2 H), 3.68 (s, 3 H), 4.16 (t, 2 H), 5.19 (s, 2 H), 6.71 (s, 4 H), 7.26 (s, 5 H); *p*-Cl 3.31 (t, 2 H), 4.29 (t, 2 H), 5.34 (s, 2 H), 6.72–7.36 (q, 4 H), 7.45 (s, 5 H).

4-(Para-substituted-phenoxy)-2-oxobutanoic Acids 1–4. Benzyl 4-(para-substituted-phenoxy)-2-oxobutanoates (10 mmol) were dissolved in 50 mL of ethyl acetate and hydrogenolyzed over Pd/C at 2.75 atm for 4 h. Solvent was removed by flash evaporation following filtration of the reaction solution through Celite. The residues 1–4 were crystallized from CCl_4 and recrystallized from hexane/benzene (7:3) to give the corresponding acids.

1 (*p*-H): 59% yield; mp 83–85 °C; NMR 3.5 (t, 2 H), 4.49 (t, 2 H), 6.92–7.75 (m, 5 H), ~8.4 (s, 1 H).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; O, 32.96. Found: C, 61.84; H, 5.17; O, 33.05.

2 (*p*-CH_3): 45% yield; mp 96–98 °C; NMR 2.30 (s, 3 H), 3.39 (t, 2 H), 4.34 (t, 2 H), 6.98 (q, 4 H), 8.4 (s, 1 H).

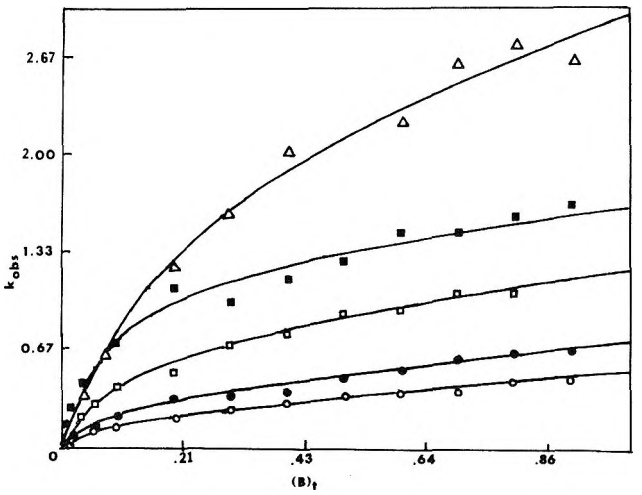


Figure 1. Plot of the pseudo-first-order rate constant, k_{obsd}, vs. the total concentration of morpholine (M) for reactions of 4-*p*-cresoxy-2-oxobutanoic acid (**2**) with that amine: ○, pH 8.0; ●, pH 8.26; □, pH 8.63; ■, pH 8.93; △, pH 9.26.

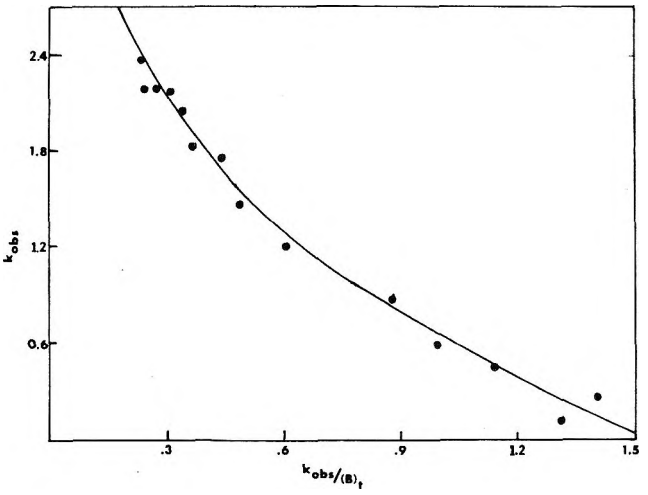


Figure 2. Eadie–Hofstee type plot of the pseudo-first-order rate constant, k_{obsd}, vs. $k_{obsd}/[\text{Morpholine}]_{total}$ for reactions of 4-phenoxy-2-oxobutanoic acid (**1**) with that amine at pH 8.92.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.44; H, 5.82; O, 30.74. Found: C, 63.52; H, 5.73; O, 30.59.

3 (*p*-CH_3O): 40% yield; mp 99–102 °C; NMR 3.23 (t, 2 H), 3.71 (s, 3 H), 4.27 (t, 2 H), 6.76 (q, 4 H), ~8.4 (s, 1 H).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.41; O, 35.68. Found: C, 58.77; H, 5.47; O, 35.67.

4 (*p*-Cl): 68% yield; mp 102–104 °C; NMR 3.36 (t, 2 H), 4.28 (t, 2 H), 6.66–7.38 (q, 4 H), ~8.4 (s, 1 H).

Anal. Calcd for $C_{10}H_9ClO_4$: C, 52.53; H, 3.98; O, 27.99. Found: C, 52.49; H, 4.35; O, 28.63.

Results

4-(Para-substituted-phenoxy)-2-oxobutanoic acids **1–4** undergo general-base-catalyzed β-elimination to give para-substituted phenols and 2-oxobutenoic acid (eq 1) in aqueous solutions of amine buffers. Spontaneous elimination at pH 7 was found to be negligible. Plots of the pseudo-first-order rate constants, k_{obsd}, vs. concentration of amine bases were curved, showing a complex dependence of k_{obsd} on the total concentration of amine base, $[B]_t$. The plots appeared to be biphasic, with an initial line of large slope at low $[B]_t$ which changed to a line of smaller slope at high $[B]_t$. A family of these plots obtained using 4-(*p*-cresoxy)-2-oxobutanoic acid (**2**) as the substrate and morpholine as the amine catalyst is shown in Figure 1.[23] A similar change in slope with change in base or

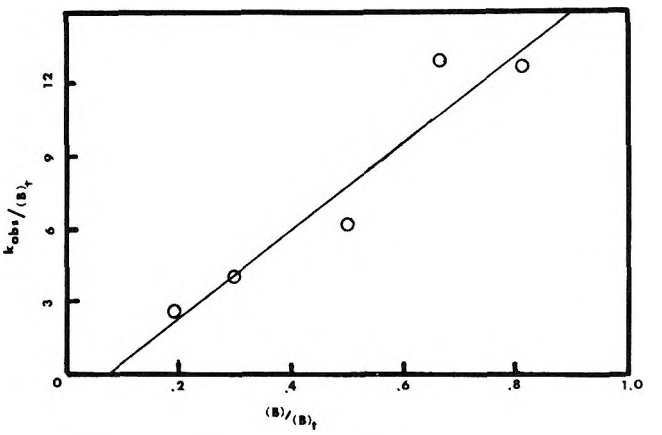


Figure 3. Plot of the pseudo-first-order rate constant, k_{obsd}, divided by the molar concentration of total morpholine vs. the fraction of the base form of morpholine for reactions of 4-*p*-cresoxy-2-oxobutanoic acid (**2**) with 0.01 M morpholine.

acid concentration has been seen for several different reactions;[24–29] including the elimination of water from 9-hydroxy-10-methyl-2-*cis*-decalone. The biphasic curve is indicative of the presence of an intermediate in the reaction, and the change in slope signifies a change in the rate-determining step of the reaction.[25]

The pseudo-first-order rate constants of the reactions were measured up to a total base concentration of 1.0 M, at which concentration the final limiting slope has not been reached and can not be easily determined and verified. It was important to determine whether the final slope had a value of 0 or more. If the final slope were 0, the shape of the k_{obsd} vs. $[B]_t$ plot would be similar to that observed by Fedor and Glave[5] in their study of the elimination of phenols from 4-(para-substituted-phenoxy)-2-butanones and could be described by eq 2, the pseudo-first-order rate equation for a simple E1cB process (Scheme I). A nonzero final slope implies more than one intermediate and/or more than one pathway for decomposition of the intermediate to product, as shown for elimination from 9-hydroxy-10-methyl-2-*cis*-decalone.[6] Two criteria were used to show that the final slopes were greater than 0. First, an Eadie–Hofstee type plot of k_{obsd} vs. $k_{obsd}/[B]_t$ will give a straight line according to eq 3, where fr_A is the fraction of free acid, for a biphasic curve with a final slope of 0. It was found that for elimination from **1** to **4** the Eadie–Hofstee plots were curved as shown typically in Figure 2. Second, a computer fit of the data obtained for reactions of **1–4** run at any constant pH to a curve described by eq 4 could be made. This equation describes the biphasic curves of Figure 1. The parameters p, q, and r are combinations of constants. The initial limiting slope, when values of $[B]_t$ are very small such that $p[B]_t \gg q[B]_t^2$, is equal to p and the final limiting slope, when values of $[B]_t$ are large such that $r[B]_t \gg 1$, is equal to q/r. Also, plots (not shown) of $k_{obsd}/[B]_t$ vs. $[B]_t$ (eq 5) are hyperbolic with finite, nonzero limits.[44]

$$k_{obsd} = k_1[B]/((k_2/k_3)[BH] + 1) \quad (2)$$

$$k_{obsd} = k_1k_3K_a/k_2a_H - (k_3/k_2fr_A)(k_{obsd}/[B]_t) \quad (3)$$

$$k_{obsd} = (p[B]_t + q[B]_t^2)/(r[B]_t + 1) \quad (4)$$

$$k_{obsd}/[B]_t = (p + q[B]_t)/(r[B]_t + 1) \quad (5)$$

We take the above results to show that the curves exemplified by those of Figure 1 are indeed biphasic and that the final slopes have values greater than 0. Table I lists values of p, q, and r for the second-order plots of eq 4 for reactions of **1–4** with amines of this study. These parameters were obtained by computer fits of the data to eq 5.

Table I. Kinetics Data According to Equation 4 for Reactions of 1–4 in Aqueous Solutions of Amine Buffers[a]

Amine	Substrate	Registry no.	pH	Fraction of free base (f_{r_B})	p	q	r	Final slope[b]	SE[c]
Morpholine	1 (H)	64114-05-2	7.99	0.190	2.72	3.33	9.88	0.737	7.17×10^{-3}
			8.26	0.304	3.98	1.75	5.90	0.296	2.75×10^{-2}
			8.62	0.500	7.20	3.77	5.5	0.687	4.20×10^{-2}
			8.93	0.671	15.0	7.02	8.05	0.872	5.33×10^{-2}
			9.26	0.814	12.4	4.03	3.59	1.12	7.79×10^{-2}
	2 (CH_3)	64114-04-1	8.00	0.193	2.84	4.92	13.5	0.366	1.02×10^{-2}
			8.26	0.304	4.53	5.52	12.7	0.433	2.28×10^{-2}
			8.62	0.500	7.30	5.48	9.40	0.582	2.24×10^{-2}
			8.93	0.671	15.3	6.35	12.0	0.529	7.89×10^{-2}
			9.25	0.810	11.3	5.50	4.61	1.19	1.3×10^{-1}
	3 (CH_3O)	64114-03-0	8.05	0.212	2.08	0.912	4.56	0.200	1.63×10^{-2}
			8.29	0.319	3.25	0.583	3.38	0.172	2.06×10^{-2}
			8.62	0.500	6.60	1.51	4.06	0.373	4.35×10^{-2}
			8.93	0.671	9.26	2.61	4.03	0.648	3.18×10^{-2}
			9.26	0.814	12.6	0.709	2.62	0.271	4.37×10^{-2}
	4 (Cl)	64114-02-9	8.01	0.197	3.59	5.67	6.78	0.836	5.07×10^{-2}
			8.26	0.304	4.47	5.74	3.86	1.49	3.06×10^{-2}
			8.62	0.500	7.90	2.68	2.18	1.23	7.30×10^{-2}
			8.93	0.671	11.2	9.55	3.41	2.80	1.04×10^{-1}
			9.26	0.814	13.9	11.5	2.65	4.36	6.29×10^{-2}
Imidazole	1 (H)		6.50	0.220	0.137	0.130	16.13	0.00804	7.29×10^{-4}
			6.86	0.392	0.169	0.0209	3.71	0.00563	2.93×10^{-2}
			7.05	0.500	0.218	0.219	6.10	0.0359	2.71×10^{-3}
			7.26	0.619	0.308	0.0628	4.69	0.0134	2.12×10^{-3}
			7.70	0.817	0.346	0.0443	2.26	0.0196	3.39×10^{-3}
Imidazole	3 (CH_3O)		7.05	0.500	0.151	0.0503	4.44	0.0113	1.66×10^{-2}
Diethanolamine	1 (H)		8.17	0.183	1.48	6.33	9.9	0.639	1.91×10^{-2}
			8.67	0.415	4.15	12.0	10.25	1.17	4.25×10^{-2}
			8.82	0.500	4.27	8.15	5.65	1.44	4.33×10^{-2}
			9.33	0.764	9.09	3.15	3.86	0.818	1.55×10^{-1}
			9.49	0.824	8.65	0.801	1.26	0.636	1.31×10^{-1}
Dimethylamino-ethanol	3 (CH_3O)		8.81	0.186	10.21	5.02	5.68	0.884	2.49×10^{0}
			9.12	0.319	19.4	8.70	5.46	1.60	1.63×10^{0}
			9.38	0.460	30.6	6.31	4.41	1.43	2.32×10^{0}
			9.76	0.670	44.7	6.15×10^{-9}	2.45	2.52×10^{-9}	1.69×10^{0}
			10.02	0.788	51.8	3.36×10^{-8}	1.93	1.74×10^{-8}	2.04×10^{0}

[a] The concentration range of base is 0.01–1.0 M; 15 k_{obsd} values/pH; 30 °C and μ 1.0 M (KCl). [b] The final slope values are erratic because of the somewhat erratic values of k_{obsd} obtained from the spectrophotometric assay when the absorbance change between 1–4 and the products is small. A single point on the k_{obsd} vs. [B] plot can make a great deal of difference in the parameter values given by the curve-fitting program. Thus, the final slope values are variable, but there are sufficient points to assure that the reported effects, e.g., positive final slopes (Figure 1), $\rho\ (k_1) \sim 0$ and $\rho\ (k_4) > \rho\ (k_3)$, are real. [c] The values of the parameters p, q, and r were those for which the sum of the squares of the differences between observed and predicted k_{obsd} values were minimized as defined by ϕ, where $\phi = \Sigma^{n}_{i=1}[Y_i - \hat{Y}_i]^2$ and Y_i is k_{obsd} (experimental) and $\hat{Y}_i$ is k_{obsd} (predicted). The standard error of estimate, SE, is $(\phi/(N-K))^{1/2}$, where N is the number of k_{obsd} values and K is the number of constants (4) to be determined; as run, the equation used was $k_{obsd} = (ax + bx^2)/(cx + d)$, and $p = a/d$, $q = b/d$, and $r = c/d$.

The data of Table I show that the initial and final slopes increase with the increasing fraction of free amine (f_{r_B}) (cf. Figure 1), which suggests that general base and not general acid catalysis is present in the limiting cases. For each base, a plot of $k_{obsd}/[B]_t$ vs. f_{r_B} obtained for different pH values was drawn using the k_{obsd} values at 0.01 M $[B]_t$. That value was chosen because it was assumed that at low base concentrations the value of k_{obsd} lies on or near to the initial slope. One of these plots is shown in Figure 3. All plots were linear and had either 0 or small negative intercepts, indicating that the initial slope indeed reflects general-base- and not general-acid-catalyzed processes; the presence of general-acid-catalyzed processes would require positive intercepts in the graphs. Since only general-base catalysis was observed, the equation of the initial line (Figure 1, eq 4) would have the form of eq 6, and any proposed mechanism for the reactions of 1–4 must have a steady-state equation which reduces to eq 6 at very low base concentrations. Similar plots were not made for final slopes because the values of k_{obsd} obtained at the highest $[B]_t$ used (1.0 M) were not on the final slope.

$$k_{obsd}\ (\text{initial}) = k_1 f_{r_B}[B]_t \qquad (6)$$

For hydroxide ion catalysis of elimination, a plot of k_{obsd} vs. a_{OH} for reactions of 4-phenoxy-2-oxobutanoic acid (1) was linear over the limited range of hydroxide activities over which the reaction rates could be monitored (Figure 4). The small intercept in the plot is statistically insignificant. The second-order rate constant for hydroxide ion catalysis was obtained from the slope of the line and is provided in Table II together with those constants for the reactions of 2–4 with one hydroxide ion concentration. Hydroxide ion catalysis was not an important contribution to the elimination reactions of 1–4 in catalytic amine buffer solutions. Values of $k_{obsd} - k_{OH}a_{OH} \simeq k_{obsd}$ for reactions in amine buffer solutions, except for values of k_{obsd} obtained for the lowest base concentration, 0.01 M, at the highest pH of a set; in these cases, the value of $k_{OH}a_{OH}$ was approximately 15% of k_{obsd}. Also, a computer fit of the data to eq 4, with the $k_{OH}a_{OH}$ term appended, invariably gave values of this latter term which were negligible in comparison with the values of the other parameters. Hy-

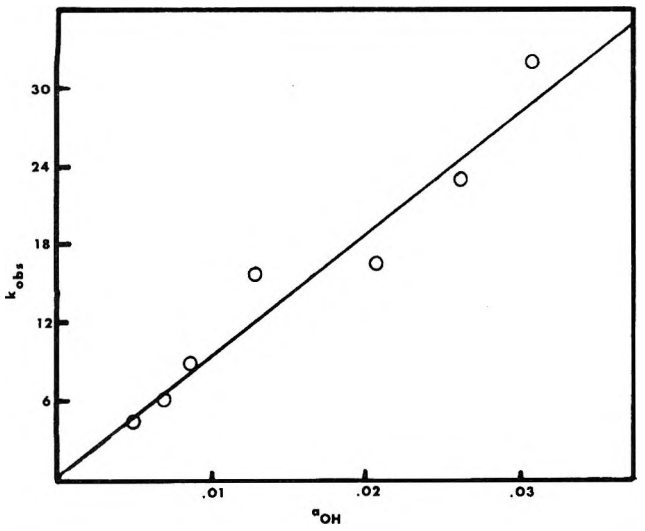


Figure 4. Plot of the pseudo-first-order rate constant, k_{obsd}, vs. the hydroxide activity, K_w/a_H, for reactions of 4-phenoxy-2-oxobutanoic acid (1) with hydroxide ion.

Table II. Rate Data for Hydroxide Ion Catalyzed Elimination Reactions of 1–4

Compd	$a_{OH} \times 10^3$	k_{obsd}, min^{-1}	k_{OH}, M^{-1} min^{-1}	No. of runs
1 (H)	4.68–51.3	4.6–41.2	934	7
2 (CH_3)	4.37	3.72 ± 0.41	851	4
3 (CH_3O)	4.37	4.12 ± 0.21	945	6
4 (Cl)	4.37	4.28 ± 0.35	980	5

droxide ion catalysis was therefore ignored in the data when amine catalysts were used, and any error in this approximation is slight and does not affect mechanistic conclusions.

Rate constants for elimination reactions of 4-(*p*-anisoxy)-2-oxobutanoic acid (**3**) in dimethylaminoethanol buffers were obtained at five pH values. At pH values below the pK_a (9.45), plots of k_{obsd} vs. $[B]_t$ were typically biphasic with a positive final slope. However, when pH exceeded pK_a, the final slopes of the plots were $\simeq 0$, as determined by computer fit of the data to the NLIN program, and the data therefore fit eq 2. At the two higher pH values, the Eadie–Hofstee type plots were found to be linear (Figure 5), as required by the fit of the data to eq 2.

Rate constants were obtained for reactions of 4-(*p*-chlorophenoxy)-2-oxobutanoic acid (**4**) with morpholine in D_2O at pD 9.01. The reactions generally gave good linear pseudo-first-order plots at very low concentrations of amine (0.01–0.02 M), but at higher amine concentrations the initial slope changed to a smaller final slope (plots not shown). Similar biphasic plots have been observed with other elimination reactions when D_2O is the solvent.[4,6] The curved plots can be explained by assuming rapid, reversible formation of a carbanion intermediate, followed by slower decomposition of the intermediate to products. For such a reaction, α-hydrogen exchange would be faster than elimination, so that at the beginning of the reaction only α,α-diprotio substrate is present, but as the reaction proceeds the concentration of the α-deuterio substrate builds until, toward the end of the reaction, only α,α-dideuterio substrate is the reactant. The curvature in the first-order plot is the result of faster elimination from the more acidic α,α-diprotio substrate than from the α,α-dideuterio substrate in D_2O; the rate of product formation thus decreases as the reaction progresses. At low concentrations of general base, as stated above, $k_{obsd} = k_1 f_B [B]_t$ and carbanion formation is rate determining (Scheme I), so that

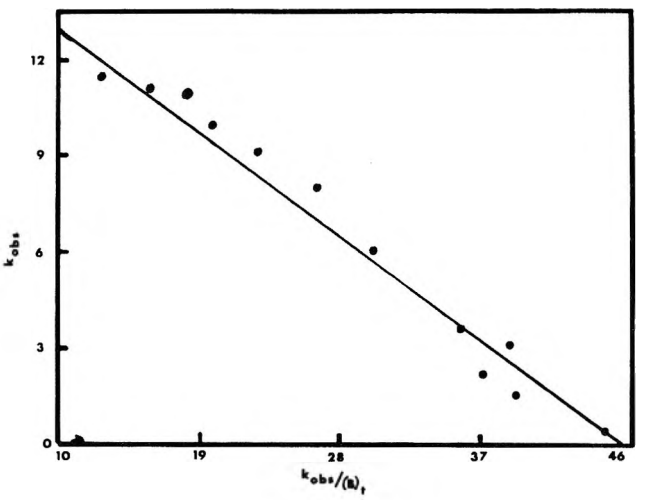


Figure 5. Eadie–Hofstee type plot of the pseudo-first-order rate constant, k_{obsd}, vs. $k_{obsd}/[\text{dimethylaminoethanol}]_{total}$ for reactions of 4-*p*-anisoxy-2-oxobutanoic acid (**3**) with that amine at pH 9.76.

Table III. Deuterium Solvent Kinetic Isotope Effects for Reactions of 4 with Morpholine[a]

$[\text{Morpholine}]_t$, M	k_{obsd}, min^{-1} (D_2O)	k_{obsd}, min^{-1} (H_2O)[b]	k_{obsd} (D_2O)/k_{obsd} (H_2O)
0.08	0.655	0.429	1.53
0.1	0.743	0.514	1.45
0.2	1.12	0.866	1.30
0.3	1.32	1.15	1.15
0.4	1.90	1.41	1.35
0.5	2.92	1.64	1.78
0.6	3.30	1.87	1.77
0.7	5.40	2.08	2.60
0.8	6.23	2.29	2.72
0.9	6.32	2.50	2.53
1.0	6.36	2.70	2.35

[a] pD 9.01 was obtained by adding 0.4 to the pH meter reading at 30 °C. [b] Calculated for morpholine-catalyzed reactions at pH 8.46.

in this case α-hydrogen exchange would not be observed and first-order plots would be linear, as was observed. The shapes of the pseudo-first-order plots offered strong qualitative evidence for the formation of a carbanion intermediate and for an E1cB mechanism. Quantitative data that was obtained was also in agreement with an E1cB mechanism. The k_{obsd} value obtained at $[B]_t = 0.01$ M was 0.0677 min^{-1} ($f_B[B]_t = 0.00409$ M).[31] The k_{obsd} value calculated from the data of Table I for the reaction of **4** with morpholine in water was 0.0652 min^{-1} ($f_B[B]_t = 0.00409$ M). At this low $[B]_t$ value, the deuterium solvent isotope effect reflects α-proton abstraction and $k(D_2O)/k(H_2O) = 1.04$, close to the value of 1.07 found by More O'Farrell and Slae[4] for α-proton abstraction in the elimination of methanol from 9-fluorenylmethanol.

When the pseudo-first-order plots were curved, at high $[B]_t$, the final limiting slopes of the plots were taken to represent the elimination from α,α-dideuterio substrate in D_2O. The rate constants were estimated by graphical determination of the limiting straight lines at long periods of time from plots of $\ln(OD_\infty - OD_t)$ vs. time. The deuterium solvent isotope effect was calculated using the calculated k_{obsd} values for elimination from α,α-diprotio-**4** in H_2O at pH 8.46 using morpholine as the base (same concentration of the base form of morpholine for each rate constant comparison), so that the estimated isotope effect represents the ratio of elimination of α,α-dideuterio-**4** in D_2O to α,α-diprotio-**4** in H_2O. The

Table IV. Rate Constants and Rate Constant Ratios for Reactions of 1–4 with Amines According to Equation 7[a]

Compd	Amine	k_1, M^{-1} min^{-1}	k_2/k_3, M^{-1}	k_3^A/k_3, M^{-1}
1 (H)	Morpholine	15.9	13.8	1.30
2 (CH_3)	Morpholine	16.2	21.1	1.78
3 (CH_3O)	Morpholine	12.5	8.47	0.489
4 (Cl)	Morpholine	16.5	6.25	2.34
1 (H)	Imidazole	0.482	12.6	0.945
3 (CH_3O)	Imidazole	0.301	8.72	0.608
1 (H)	Diethanolamine	9.79	10.3	3.43
3 (CH_3O)	Dimethylaminoethanol	62.9	7.17	0.548

[a] Average of five values, except for the reactions of 3 with imidazole (1 value) and with dimethylaminoethanol (5 values of k_1 and 3 values of k_2/k_3 and k_3^A/k_3) (pH 8.8, 9.12, and 9.38).

Scheme II

$$1\text{–}4 \underset{k_2,\ BH}{\overset{k_1,\ B}{\rightleftharpoons}} (1\text{–}4)^- \xrightarrow{k_3,\ k_3^A,\ BH} \text{products}$$

isotope effects obtained in this manner are approximate since there is no way of telling if the limiting condition of complete exchange was ever reached. These data are listed in Table III. The data show that at most concentrations of morpholine the solvent isotope effect was approximately 1.4–1.7, although the values were higher at higher $[B]_t$. Taken as a group, these isotope effects are closer to those reported for E1cB mechanisms than for concerted E2 processes; E1cB-type elimination of methanol from β-methoxy ketones from β-phenoxyethyldimethylsulfonium iodide gave solvent isotope effect values of 1.15–1.3[32] and 1.52,[33] respectively, and E2-type elimination should give a solvent isotope effect of less than 0.5.[1,4,32]

Discussion

The kinetics results obtained for the general-base-catalyzed elimination of para-substituted phenols from 1–4 indicate the operation of a E1cB mechanism. The curvilinear k_{obsd} vs. $[B]_t$ plots (Figure 1) are strong evidence for an intermediate in this reaction, and the carbanionic nature of that intermediate is supported by the deuterium solvent isotope data. The curvilinear plots for the reactions of 4 with morpholine in D_2O strongly indicate that α-hydrogen exchange is faster than elimination at high base concentrations, and the magnitude of the isotope effects is consistent with an E1cB mechanism. A possible mechanism for this reaction is outlined in Scheme II, which is a variant of the simple E1cB mechanism of Scheme I.

In order to accommodate the final nonzero slope (Figure 1, Table I), a general-acid-catalyzed pathway for carbanion decomposition is postulated to occur simultaneously with the uncatalyzed pathway to products. The steady-state equation for Scheme II is eq 7. At the limits of low and high amine concentration, the equation reduces to two linear equations, eq 6 at low amine concentrations and eq 8 at high amine concentrations. The constant k_1 and the rate constant ratios k_2/k_3 and k_3^A/k_3 were calculated from eq 6, 7 and 8 and the data of Table I and are provided in Table IV. Hammett ρ' values, obtained for the reactions of 1–4 with morpholine, may be computed from these data, and we have used ρ' as a guide to the reaction mechanism.[34]

$$k_{obsd} = (k_1[B] + (k_1k_3^A/k_3)[B][BH])/(k_2/k_3 + k_3^A/k_3)[BH] + 1) \quad (7)$$

$$k_{obsd}\ (final) = (k_1k_3^A/(k_2 + k_3^A)[B] + (k_1k_3K_a/(k_2 + k_3^A)K_w)a_{OH}) \quad (8)$$

The dependence of k_1 and k_2/k_3 on electronic effects of para substituents in 1–4 is also consistent with the E1cB mechanism of Scheme II. The rate constant k_1 is quite insensitive to electronic effects of para substituents (ρ' 0.085), as anticipated for carbanion formation at a site remote from the substituents. As for k_2/k_3, it would be anticipated that the ratio would decrease with increasing σ' value; the rate of protonation of carbanions $(1\text{–}4)^-$ to re-form 1–4 should decrease slightly while k_3 should increase appreciably with an increase in σ'. Indeed, the predicted decrease in k_2/k_3 was observed (ρ' −0.8). The mechanism of Scheme II also features general acid catalysis for the breakdown of carbanion to products, as was proposed for the dehydration of 9-hydroxy-10-methyl-2-*cis*-decalone.[6] However, such catalysis should be much less important for 1–4 than for the 2-decalone because phenols–phenoxide ions are much better leaving groups than water–hydroxide ions. For elimination from 4-(para-substituted-phenoxy)-2-butanones,[5] there is no evidence to support the existence of a general acid pathway from carbanions to products, and based on the concept[35] that general acid–base catalysis will occur where most needed and in a manner such that unstable species are not produced, general acid catalysis for the breakdown of 1–4 carbanions would not be expected. Also, experimental evidence disfavors this feature of mechanism. The ratio k_3^A/k_3 (Table IV) should decrease with an increase in the electron-withdrawing power of para substituents. However, the ratio increases (ρ' 0.5). These considerations suggest that an alternative mechanism for the reactions of 1–4 would be more appropriate.

Scheme III (not shown) is Scheme I with an additional pathway from 1–4 to products, which is a concerted general-base-catalyzed pathway ($k_4[B]$). Scheme III gives a steady-state equation which has the same form as eq 4, namely eq 9. The scheme involves the simultaneous occurrence of E1cB- and E2-type reactions as proposed by More O'Farrell[36] for the elimination of methanol from 9-fluorenylmethanol. On theoretical grounds and on the basis of the deuterium solvent isotope effect results, we disfavor the mechanism of Scheme III. As Jencks[37] has pointed out, the primary reason for a concerted mechanism such as an E2 mechanism lies in the avoidance of highly unstable intermediates that would be required for a stepwise mechanism. If such an unstable intermediate were present in the elimination of 1–4 it would be much more likely to decompose than to exchange an α-hydrogen for deuterium. The results of this study indicate that exchange can be faster than elimination. Also, we call attention to the result that at pH 9.76 and 10.02 elimination from 2 catalyzed by dimethylaminoethanol can be adequately described by the mechanism of Scheme I. This is equivalent to saying that there is a loss of the E2 pathway as the pH is raised within the same buffer series, and there is no reason why this should happen. However, to the extent that the experimental result may be artifactual (vide infra), this argument against Scheme III is less compelling.

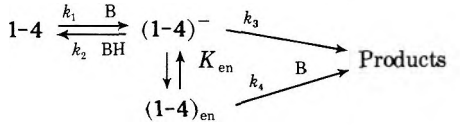
$$k_{obsd} = ((k_1 + k_4)[B] + (k_2k_4/k_3)[B][BH])/((k_2/k_3)[BH] + 1) \quad (9)$$

An alternative mechanism which we favor is that of Scheme IV which features a rapid equilibrium between carbanions and

Table V. Calculated Rate Constants for the Mechanism of Scheme IV

Compd	pK_{SH}	k_2, M^{-1} min^{-1}	k_3, min^{-1}	k_4/K_{en}, min^{-1}	σ'
1 (H)	13.20	6.11×10^5	4.42×10^4	2.39×10^{13}	0
2 (CH_3)	13.21	6.30×10^5	2.98×10^4	2.21×10^{13}	−0.16
3 (CH_3O)	13.25	5.37×10^5	6.34×10^4	1.29×10^{13}	−0.23
4 (Cl)	13.09	4.93×10^5	7.88×10^4	7.68×10^{13}	0.6

Scheme IV



enols, as postulated by Hupe et al.[6] for the dehydration of 9-hydroxy-10-methyl-2-*cis*-decalone; spontaneous decomposition of carbanions and general-base-catalyzed decomposition of enols gives products. The steady-state equation for Scheme IV is given by eq 10. In eq 10, the initial slope is still k_1 (Table IV), the ratio k_2/k_3 is the same as that calculated from eq 9 of Scheme III (Table IV), and the ratio k_4K_a/K_{en} is mathematically equivalent to the rate constant k_3^A of Scheme III. However, in contrast to the predicted dependence of the ratio k_3^A/k_3 in Scheme III on the Hammett σ' values, the ratio k_4K_a/k_3K_{en} of Scheme IV should increase with an increase in the electron-withdrawing properties of para substituents, as is the case. We computed ρ' values for k_2, k_3, and k_4/K_{en} based on the calculated values of these constants. Although the computed values are likely incorrect because they are based on the ionization constants (K_{SH}) of **1–4**, which must be estimated, their relative values are likely correct since they are based on experimental values, and the ρ' values should be correct as well. From the relationship $k_1/k_2 = K_{SH}/K_a$,[6] the assumption that K_{SH} (1–4)/K_{SH} (4-aryloxy-2-butanones) = K_{SH}(pyruvic acid)/K_{SH}(acetone) = $k_{enolization}$(pyruvic acid)/$k_{enolization}$(acetone), and the data of Table IV, the necessary constants may be calculated. Schellenberger and Hubner[38] have measured the ratio of rate constants for the general-base-catalyzed enolization of pyruvate and acetone; its value is 17.5. The values of K_{SH} for **1–4** were therefore assumed to be 17.5 times greater than those estimated for 4-aryloxy-2-butanones.[6] Table V gives the values of the constants from which ρ' (k_2) = −0.09, ρ' (k_3) = 0.3, and ρ' (k_4/K_{en}) = 0.8 may be computed.

Although the correlation coefficients of the regressions are not very good (r = 0.62–0.98), the resultant ρ' appear to be reasonable for the mechanism of Scheme IV. We assume that $\rho'(k_4/K_{en})$ essentially reflects electronic effects on the k_4 step. An interesting aspect of this exercise is the result that elimination from enols via k_4 is more sensitive to electronic effects than is elimination from enolates via k_3. This would be true if the extent of C–O bond breaking in the transition state for elimination from enols was greater than that for elimination from enolates. Noting that **1–4** exist as carboxylate anions in morpholine buffer solutions, we believe that the enolate dianion would be a high-energy intermediate, and elimination from it would involve an early transition state. On the other hand, the enol could be well stabilized via ion-reinforced hydrogen bonding, and elimination from it could well involve a later transition state. Here it is well to point out that elimination from enols of 4-aryloxy-2-butanones appears not to be kinetically important, which may reflect the lessened stability of these enols relative to those of **1–4**. Also, ρ' (k_3) for 4-aryloxy-2-butanones should be greater than ρ' (k_3) for **1–4**, and this is the case.

$$k_{obsd} = (k_1[B] + (k_1k_4K_a/k_3K_{en})[B][BH])/((k_2/k_3 + k_4K_a/k_3K_{en})[BH] + 1) \quad (10)$$

Further support for the mechanism of Scheme IV may be found in a literature analogy for general base catalysis of proton transfer from enol OH. Hegarty and Jencks[39] recently examined the product term, k_{AB}[acid][base], for the enolization of acetone, and they concluded that the most likely involvement of the acid–base pair is in concerted proton transfer. The reverse ketonization reaction then involves concerted proton transfer from enol OH to a general base and from general acid to an enolic carbon. If this conclusion is correct, then postulated enols of this study could well employ general base catalysis of proton transfer from enol OH and achieve a stable configuration (products) by transferring electrons to the leaving aryloxide ion rather than to a general acid. On theoretical grounds, the incursion of general base catalysis in the k_4 step could be predictable on the basis that conversion of the enol to products involves a pK change of greater than 15, with formation of the unstable keto-protonated 2-oxobutenoic acid; proton transfer during elimination would avoid formation of this unstable product.[37,40]

For reactions of **3** in dimethylaminoethanol, the change in the limiting slope at high amine concentrations to approximately 0 (Table I) at pH 9.76 and 10.02 remains questionable; in terms of the mechanism of Scheme IV, it is as if the k_4 step has diminished to the point of undetectibility. We attempted to address the question by examining the consistency of the data by computing various rate constants or rate constant ratios of equation 10 using that equation, eq 4, and the data of Table I. For the five pH values, k_1 = 62.9 ± 5.1 M^{-1} min^{-1}. For pH 8.81, 9.12, and 9.38, k_2/k_3 = 6.64, 7.39, and 7.78 M^{-1}, and the value of k_4K_a/k_3K_{en} is ~7% of the term (k_2/k_3 + k_4K_a/k_3K_{en}). If the k_4-containing term is ignored and k_2/k_3 is calculated for pH 9.76 and 10.02, the values are 7.66 and 9.13 M^{-1}, not significantly different from those values obtained for lower pH's. All five values of the set give k_2/k_3 = 7.68 ± 0.97 M^{-1}. The k_1 and k_2/k_3 values may be compared with those of 4-anisyloxy-2-butanone, which are 5.49 M^{-1} min^{-1} and 7.8 M^{-1} min^{-1}, respectively.[6] The data thus seem to be consistent, and we may conclude that the apparent loss of the k_4 term is the result of general-base-catalyzed conversion of enol to products becoming noncompetitive with spontaneous conversion of enolate to product as pH is raised. At high concentrations of dimethylaminoethanol buffer (~1 M), the $q[B]_t^2$ term constitutes ~30 (pH 8.81) to 10% (pH 10.02) of the numerator term of eq 4; the k_4K_a/k_3K_{en} part of the $r[B]_t$ term remains at ~7% of this denominator term over the pH range of the experiments. Arithmetically, the k_4-containing terms become increasingly difficult to detect as pH increases.

It appears to us that, of the three possible schemes presented, Scheme IV is the most reasonable on experimental and theoretical grounds. For the mechanism of Scheme IV, the general-acid-catalyzed formation of enol directly from **1** to **4** might be expected, since this is a known reaction.[35] However, the plots of $k_{obsd}/[B]_t$ vs. f_{rB} (Figure 3) imply that the formation of an intermediate (s) is not general acid catalyzed to any great extent. In this regard, previous studies of the enolization of α-keto acids have shown that enolization is predominantly general base catalyzed; both Schellenberger and Hübner[38] and Hegazi and Meany[41] found that enolization of pyruvic acid is not acid catalyzed to any great extent. Analogously, general acid catalysis for enolization of **1–4** would not necessarily be expected, and the mechanism of Scheme IV

remains reasonable.[45]

Finally it is interesting to speculate on the reason why **1–4** undergo elimination by a mechanism that is more complex than the mechanism of elimination of 4-aryloxy-2-butanones (Scheme I).[6,43] It might be reasonable for **1–4** to undergo elimination via an enol intermediate, while the corresponding ketones would not undergo such an elimination if the enol form of **1–4** would be more stable relative to the keto form than would the enol form of 4-aryloxy-2-butanones. A more stable tautomer would mean that it would be more energetically favorable for enolate anions to react to form enol rather than collapse back to keto tautomers in the initial steps before product is formed. A quantitative measure of the relative stabilities of the various tautomers is the keto–enol tautomerism equilibrium constant. The constants have not been measured for **1–4** or for the corresponding 4-aryloxy-2-butanones, but equilibrium constants for analogous compounds can give some insight into the stability of the enols. The equilibrium constant for enolization of acetone, calculated from the data of Schwarzenbach and Wittwer,[42] is 2.5×10^{-6}. From the data of Schellenberger and Hübner,[38] the equilibrium constant for enolization of 2-oxobutanoic acid is 6.6×10^{-3}. The 10^3 difference in equilibrium constants is a significant indicator that formation of enol from enolate would be more likely for **1–4** than for 4-aryloxy-2-butanones.

Acknowledgment. We wish to thank Mr. William Hendricks for his assistance in obtaining the primary kinetic data. This work was supported in part by a grant from the U.S. Public Health Service.

Registry No.—Benzyl diethoxyacetate, 64114-01-8; diethoxyacetic acid, 20461-86-3; benzyl chloride, 100-44-7; 2-carbobenzoxy-1,3-dithiane, 64114-00-7; 1,3-propanedithiol, 109-80-8; *p*-bromophenetole, 589-10-6; *p*-methyl-β-bromophenetole, 18800-34-5; *p*-methoxy-β-bromophenetole, 22921-76-2; *p*-chloro-β-bromophenetole, 2033-76-3; 2-(β-phenoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-99-1; 2-(β-*p*-cresoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-98-0 2-(β-*p*-anisoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-97-9; 2-(β-*p*-chlorophenoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-95-7. benzyl 4-phenoxy-2-oxo-butanoate, 64113-96-8; benzyl 4-(*p*-cresoxy)-2-oxobutanoate, 64113-94-6; benzyl 4-(*p*-anisoxy)-2-oxobutanoate, 64113-93-5; benzyl 4-(*p*-chlorophenoxy)-2-oxobutanoate, 64113-92-4.

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(44) We examined some solvent and salt effects to test if the nonzero final slopes (Figure 1) are due to such effects. For reactions of 4-*p*-cresoxy-2-oxobutanoic acid (**2**) in 0.05 M morpholine buffer, pH 8.13, the k_{obsd} (min^{-1}) and total salt, morpholine hydrochloride and potassium chloride, concentrations (M) are as follows: 0.130, 0.1; 0.121, 0.2; 0.121, 0.3; 0.127, 0.5; 0.139, 0.7; 0.127, 0.9. Thus, k_{obsd} is little affected by changes in KCl concentration in the range 0.1–0.9 M. Replacement of KCl with tetramethylammonium chloride (TMAC) slightly decreased k_{obsd} for elimination in 0.05 M morpholine, pH 8.22, μ 1.0 M (KCl + TMAC). k_{obsd}, [TMAC] are: 0.123, 0; 0.121, 0.1; 0.115, 0.2; 0.109, 0.4; 0.101, 0.6; 0.101, 0.8. The use of 1,4-dioxane as a cosolvent had either no effect on k_{obsd} or else caused a decrease in its value. For reactions of **2** with 0.05 M morpholine in aqueous dioxane, pH 8.16 and μ 1 M (KCl), k_{obsd} (min^{-1}) and dioxane concentrations (M) are as follows: 0.121, 0; 0.119, 0.1; 0.111, 0.2; 0.103, 0.4; 0.109, 0.6; 0.130, 0.8. For 0.25 M morpholine, pH 8.16, the values are as shown: 0.313, 0; 0.330, 0.1; 0.280, 0.2; 0.285, 0.3; 0.272, 0.4; 0.253, 0.5. For 1 M morpholine, pH 8.90, the values are the following: 2.22, 0; 1.92, 0.2; 1.73, 0.4; 1.64, 0.6; 1.49, 0.8; 1.39, 1.0. For 0.2 M morpholine, pH 8.90, the values are as follows: 1.08, 0; 1.01, 0.2; 0.979, 0.4; 0.829, 0.8; 0.748, 1.2; 0.576, 1.6.
(45) We believe that elimination from **1–4** via imminium ions may play at most a very minor role in the chemistry of this study: (1) No intermediates were detected spectroscopically using **1** in morpholine buffers. (2) Rate constants have values in accord with predictions based on the results of elimination from 4-(para-substituted-phenoxy)-2-butanones.[5] (3) The kinetics of elimination of phenol from **1** catalyzed by *N*-ethylmorpholine are similar to those of this study. Data were not reported for the runs done at two pH values because amine solutions became yellow on standing. (4) The kinetics of elimination from **1** catalyzed by trifluoroethylamine (J.M.H., Ph.D. Thesis) are different from those reported here, and they resemble those reported by Hupe et al.[46,47] for covalent catalysis of elimination from 9-acetoxy-10-methyl-*cis*-decal-2-one. (5) The kinetics of elimination from **1** catalyzed by ethanolamine (J.M.H., Ph.D. Thesis) resemble those of **1–4** of this study but the pH dependence of the rate constants is not that predicted by eq 10; e.g., k_1 has an apparent acidity dependence. In regard to this last point, isomerization of 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one to the conjugated steroid is markedly catalyzed by aminoethanol while it is sluggishly transformed by tertiary amine, and the kinetics of the aminoethanol reaction resemble those of **1** in aminoethanol buffer solutions (S. Perera and L. Fedor, unpublished results).
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Linear Free-Energy Relationships in Electrophilic Addition Reactions of Alkenes. Use of Addition of Arenesulfenyl Chloride and Hydration as Mechanistic Models of Bromination[1]

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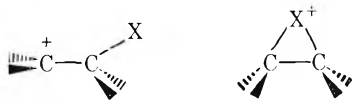
Received April 21, 1977

The use of the structure–reactivity profiles of the addition of arenesulfenyl chloride and hydration of alkenes are proposed as models of reactions involving bridged and open-ion-like rate-determining transition states, respectively. Using these reactions as standards, it is possible to obtain information on the structure of the rate-determining transition states of other electrophilic addition reactions. This method is illustrated by applying it to the electrophilic bromination of alkenes.

Linear free-energy relationships have been used frequently in studies of the mechanisms of organic reactions.[2] For electrophilic addition reactions, Hammett correlations have been the most successful of such relationships.[3] Use of the Taft correlation for electrophilic additions to alkyl-substituted ethylenes has been less successful. In general, as the number of alkenes to be correlated and their structural complexity increases, such correlations become increasingly unsatisfactory.[4] Attempts to improve the Taft correlation by defining a new substituent steric parameter, E_s^*,[5] or by introducing multiple parameters[6] have not been particularly successful. Thus far, linear free-energy relationships have been of limited use in establishing the structure of the rate-determining transition states of electrophilic addition reactions.

The fundamental problem is that there are more variables affecting the structure of the rate-determining transition state of electrophilic additions than in the reactions defining the Taft substituent constants. For example, the transition states of electrophilic additions may vary from those resembling an open ion **1** to those resembling a bridged ion **2**. Clearly one set

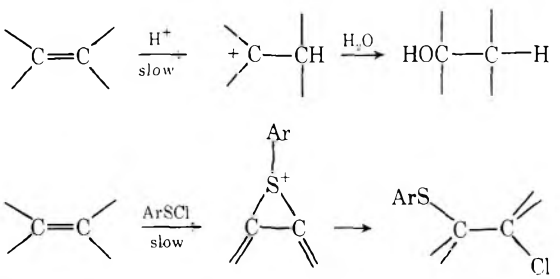


1 **2**

of substituent steric and polar parameters is inadequate, since the effects of substitutents in these two transition states are different. Also, the ground and transition states of these reactions may be affected by such variables as intra- and intermolecular steric effects, solvent effects, and electronic effects in ways that differ from those for which the substituent constants are defined.

One solution to this problem is to choose reactions to serve as models of the structure reactivity relationship for the two extreme mechanisms proceeding through transition states **1** and **2**. These reactions then become the standards against which the structure–reactivity relationship of other electrophilic addition reactions can be compared. In this way, it should be possible to establish if the rate-determining transition state for a particular reaction more closely resembles structure **1** or **2**.

The following reactions have been chosen as models. Protonation of alkenes in acid-catalyzed hydrations has been established to proceed by an open ion through the entire range of reactivity and is the best example of the first class of reaction.[3a,7] The addition of sulfenyl halides to alkenes is a reaction which proceeds through a bridged transition state for the entire range of reactivity and is the best example of the second category. The mechanism of the hydration reaction is supported by the correlation of rates with structure, solvent isotope effects, acidity dependence, and other kinetic criteria.[3a,7] The mechanism of sulfenyl halide addition is securely based on rate–structure correlations, product stereochemistry, and direct observation of thiiranium ions.[7]



A reaction suitable for study by this method is bromination. This is a reaction which has received an enormous amount of attention. While its mechanism is reasonably well established, there is still some ambiguity regarding its rate-determining transition-state structure.

Results and Discussion

The rate constants of acid-catalyzed hydration ($k_2^{H^+}$), bromination in methanol containing 0.2 M NaBr ($k_g^{Br_2}$), and addition of 4-chlorobenzenesulfenyl chloride in 1,1,2,2-tetrachloroethane (k_2^{ArSCl}) for a group of alkenes of representative structural types are given in Table I. The second-order rates of hydration were obtained by dividing the observed rates extrapolated to $H_0 = 0$ by the acidity function h_0 for that acidity.[3a-c] The second-order rates of bromination are actually a mixture of two terms: the usual second-order term, first order in both alkene and bromine, and a third-order term, first order in alkene, bromine, and bromide ion. Under the experimental conditions, the term involving bromide ion is kinetically unimportant despite its large concentration in solution.[8] Thus, $k_g^{Br_2}$ reflects the effect of alkene structure on the second-order term.

In Figure 1, $\log k_2^{H^+}$ is plotted against $\log k_g^{Br_2}$. While the points can be fitted to a line, the correlation is poor. Rather than defining one line, the points are grouped into two regions. One group of alkenes, which forms tertiary carbonium ions, is found between the values of −3 and −4 for $\log k_2^{H^+}$, while the other group, which forms secondary carbonium ions, is found between the values of −6 and −7.6. Even within these groups, there does not appear to be a direct correspondence between reactivity in bromination and reactivity in hydration. Ethylene (**3**), which has been proposed to form the primary ethyl carbonium ion,[3b] falls outside both of these groups. It is thus clear from Figure 1 that there is no similarity in the structure–reactivity profiles of hydration and bromination of alkenes. Therefore, the rate-determining transition states for the bromination of the compounds in Figure 1 do not resemble an open-ion structure throughout the range of reactivity.

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Table I. Rates of Hydration, Bromination, and Addition of 4-Chlorobenzenesulfenyl Chloride[j] to Alkenes at 25 °C

Alkene	Registry no.	Compd no.	k_2^{ArSCl},[a] M^{-1} s^{-1}	$k_g^{Br_2}$,[b] M^{-1} s^{-1}	$k_2^{H^+}$,[c] M^{-1} s^{-1}
CH_2=CH_2	74-85-1	**3**	65	0.505	0.15×10^{-1}[d]
CH_3CH=CH_2	115-07-1	**4**	205	30.7	0.238×10^{-8}
EtCH=CH_2	106-98-9	**5**	248	48.3	
i-PrCH=CH_2	563-45-1	**6**	140	28.3	
t-BuCH=CH_2	558-37-2	**7**	95	13.4	
n-BuCH=CH_2	592-41-6	**8**	133	31.7	0.432×10^{-8}
$(CH_3)_2C$=CH_2	115-11-7	**9**	550	2 730	0.37×10^{-3}
$(Et)_2C$=CH_2	760-21-4	**10**	372	4 500	
$(t\text{-Bu})_2C$=CH_2	5857-68-1	**11**	3.17×10^{-2}	12.8	
$Et(CH_3)C$=CH_2	563-46-2	**12**	611	4 470	0.522×10^{-3}
i-$Pr(CH_3)C$=CH_2	563-78-0	**13**	420	1 620	
t-$Bu(CH_3)C$=CH_2	594-56-9	**14**	147	490	0.20×10^{-3}
(c)CH_3CH=$CHCH_3$	590-18-1	**15**	1340	1 310	8.32×10^{-8}
(*t*)CH_3CH=$CHCH_3$	624-64-6	**16**	434	847	3.51×10^{-8}
(c)EtCH=CHEt	7642-09-3	**17**	3563	3 250	1.78×10^{-7}
(*t*)EtCH=CHEt	13269-52-8	**18**	388	1 850	2.11×10^{-7}
(c)EtCH=$CHCH_3$	627-20-3	**19**	2690	2 100	
(*t*)EtCH=$CHCH_3$	646-04-8	**20**	568	1 330	
(c)*i*-PrCH=$CHCH_3$	691-38-3	**21**	2624	773	
(*t*)*i*-PrCH=$CHCH_3$	674-76-0	**22**	325	600	
(c)*t*-BuCH=$CHCH_3$	762-63-0	**23**	1029	650	
(*t*)*t*-BuCH=$CHCH_3$	690-08-4	**24**	162	79.5	
(c)*i*-PrCH=CHEt	15840-60-5	**25**	2769	742	
(*t*)*i*-PrCH=CHEt	692-24-0	**26**	245	555	
(c)*t*-BuCH=CHEt	690-92-6	**27**	1704	998	
(*t*)*t*-BuCH=CHEt	690-93-7	**28**	121	108	
$(CH_3)_2C$=$CHCH_3$	513-35-9	**29**	3030	66 700	2.15×10^{-4}
(*Z*)-$Et(CH_3)C$=$CHCH_3$	922-62-3	**30**	4835[e]	79 200	
(*E*)-$Et(CH_3)C$=$CHCH_3$	616-12-6	**31**	2284[e]	75 700	
t-BuCH=$C(CH_3)_2$	107-40-4	**32**	1462[e]	13 720	
$(CH_3)_2C$=$C(CH_3)_2$	563-79-1	**33**	7760	91 700	3.42×10^{-4}
C_6H_5CH=CH_2	100-42-5	**34**	62	84.8	0.240×10^{-6}
$C_6H_5(CH_3)C$=CH_2	98-83-9	**35**	265	113	0.133×10^{-3}
(*t*)C_6H_5CH=$CHCH_3$	873-66-5	**36**	118	170	1.12×10^{-7}
(*t*)C_6H_5CH=CHC_6H_5	103-30-0	**37**	8.05	0.545	0.71×10^{-10}
$(C_6H_5)_2C$=CH_2	530-48-3	**38**	20.1	1 670	
(c)PrCH=CH_2	693-86-7	**39**	410[h]	>10^6[g]	0.254×10^{-3}
Cyclohexene	110-83-8	**40**	786[h]	11 400[i]	0.443×10^{-7}

[a] Values were obtained from ref 4a and 4b unless otherwise noted. [b] Values were obtained from ref 4c unless otherwise noted. Units changed to s^{-1}. The rate constant k_g is a global rate constant and is equal to $k_{Br_2} + Kk_{Br_3} - [Br]/(1 + K[Br^-])$. [c] Values were obtained from ref 3a–d unless otherwise noted. [d] As discussed in ref 3b, this rate is artificially low due to the method of extrapolation. However, ethylene is at least 10^4 times less reactive than propene. [e] C. L. Dean, D. G. Garratt, and G. H. Schmid, unpublished data. [f] Calculated from $k_g(1 + K[Br^-]) = k_{Br_2} + Kk_{Br_3} - [Br^-]$, E. Bienvenue-Goetz and J. E. Dubois, *J. Org. Chem.*, **40**, 221 (1975). [g] D. G. Garratt, A. Modro, K. Oyama, G. H. Schmid, T. T. Tidwell, and K. Yates, *J. Am. Chem. Soc.*, **96**, 5295 (1974). [h] Reference 11. [i] J. E. Dubois and P. Fresnet, *Tetrahedron Lett.*, 2195 (1974). [j] Registry no.: 933-01-7.

In Figure 2, log k_2^{ArSCl} is plotted against log $k_g^{Br_2}$. Here a reasonable straight line is obtained. Three compounds, cyclopropylethylene (**39**), 1,1-diphenylethylene (**38**), and 1,1-di-*tert*-butylethylene (**11**), lie far off the line and the latter is off the figure. The latter two compounds are subject to severe steric problems which appear to be especially acute in the addition of 4-chlorobenzenesulfenyl chloride to **11**. The remaining data can be correlated by eq 1 where $r = 0.849$. The dashed line represents this equation in Figure 2. A better correlation, eq 2, can be obtained by omitting compounds **15, 17, 19, 21, 23, 35,** and **27,** all cis alkenes. The solid line in Figure 2 represents this equation where $r = 0.935$.

$$\log k_2^{ArSCl} = 0.412 \log k_g^{Br_2} + 1.52 \quad (1)$$

$$\log k_2^{ArSCl} = 0.392 \log k_g^{Br_2} + 1.44 \quad (2)$$

However, the object of such plots is not to obtain the best correlation by eliminating part of the data but rather to discern trends in the structure–reactivity profile of *all the available data.* Indeed, it is the compounds that do not fit such correlations that are often the most interesting and mechanistically informative. Using this approach, the data

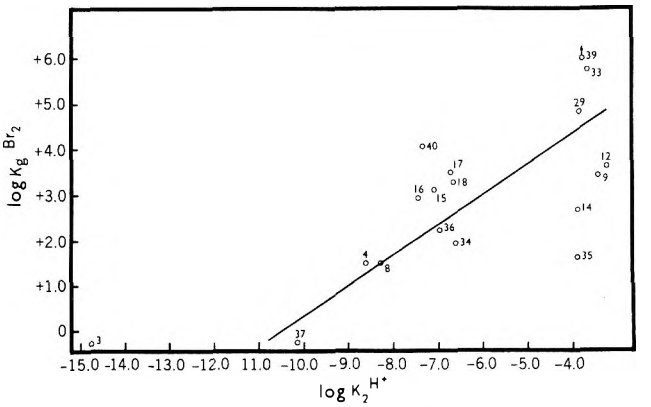

Figure 1. Plot of log $k_2^{H^+}$ vs. log $k_g^{Br_2}$. The least-square line for all points except no. 39 is log $k_2^{H^+}$ = 1.50 log $k_g^{Br_2}$ − 10.50; $r = 0.789$.

are quite informative as to the significant influences on the reactivity.

The general trend of the data in Figure 2 establishes the similarity in the structure–reactivity profiles of the additions

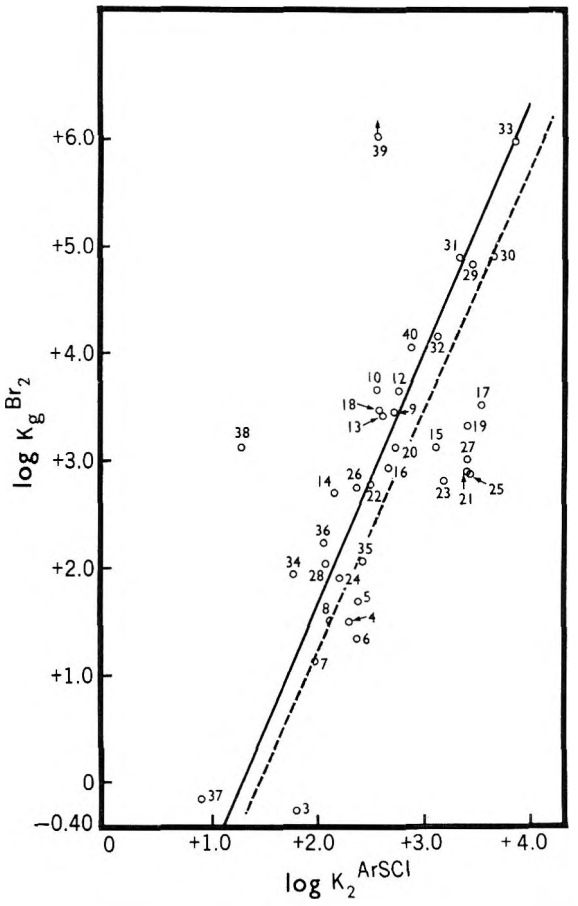

Figure 2. Plot of log k_2^{ArSCl} vs. $k_g^{Br_2}$. The dashed line represents eq 1 while the solid line represents eq 2.

of bromine and arenesulfenyl chloride. This is in accord with a general mechanism involving a bridged rate-determining transition state for both reactions. The effect of substituents is greater on the rate of bromination than on the rate of sulfenyl chloride addition. This has been previously noted for a more limited set of compounds.[4a]

Deviations from the correlation by compounds, such as cyclopropylethylene, 1,1-diphenylethylene, and 1,1-di-*tert*-butylethylene, suggest that either they react by a different mechanism or unusual steric or polar factors are present in their rate-determining transition states.

The high rate of bromination of cyclopropylethylene may be explained by a mechanism involving an open-ion-like rate-determining transition state. Consistent with this view is the formation of ring-opened products.[9] This change in mechanism is due to the great ability of a cyclopropyl group to stabilize an adjacent carbonium ion by resonance electron donation.[10] Enhancing this effect is the inability of the cyclopropyl ring to stabilize a bridged ion, since its inductive effect is electron withdrawing. Bromination of 1-cyclopropylpropene and 1,1-dicyclopropylethylene is also too fast to measure.[11]

For 1,1-diphenylethylene, the deviation results from either an enhanced bromination rate or a decreased rate of sulfenyl chloride addition. The mechanism has been proposed to involve an open-ion-like rate-determining transition state[12] in bromination which would account for its deviation. However, steric retardation cannot be ruled out. Severe steric hindrance between the *tert*-butyl groups and the electrophile (either bromine or arenesulfenyl chloride), resulting in an abnormally slow rate of addition, appear likely to be responsible for the deviation of 1,1-di-*tert*-butylethylene from the correlation.[13,14]

Correlations such as those in Figure 2 define "normal" structure–reactivity behavior and enable us to recognize "abnormal" behavior. For example, it has been known for many years that the ratio $k_{cis}/k_{trans} > 1$ for the addition of bromine and arenesulfenyl chlorides to aliphatic isomeric alkenes. However, it is never been possible to establish whether addition to the cis or trans series is abnormal. From Figure 2, it appears that the cis series deviates from the main body of data. This deviation is not due to a change in the mechanism, since all evidence is in accord with a mechanism involving a bridged rate-determining transition state for addition to all these alkenes. The deviations arises from either an abnormal rate of sulfenyl chloride addition or a diminished rate of bromination of the cis alkenes. It does not appear that the bromination rates would be retarded and instead it appears that addition of sulfenyl chloride is favored.

Another example of the mechanistic value of Figure 2 is the case of additions to styrene (**34**), 2-phenylpropene (**35**), *trans*-1-phenylpropene (**36**), and stilbene (**37**). It has been claimed that the rate-determining transition state for bromination of these compounds resembles an open 2-bromocarbonium ion.[12] If this were the case, serious deviations would be expected as in the case of 1,1-diphenylethylene. The fact that the phenyl-substituted alkenes correlate well with the aliphatic alkenes is strong evidence for a bridged rate-determining transition state. The products which are formed by nonstereospecific addition must result from an open ion formed after the rate-determining step.

The preceding examples illustrate the utility of this method. Correlations such as those in Figures 1 and 2 are based upon the assumption that the mechanisms of the model reactions do not change with changes in alkene structure. This assumption is justified by the results of extensive studies on hydration and arenesulfenyl chloride additions of alkenes. So far no exceptions to their general mechanisms have been found.

Thus, the use of the structure–reactivity profiles of these two model reactions provides a valuable method of obtaining information of the structure of the rate-determining transition state. It can be used to test other reactions such as oxymercuration[16] and thallation in which there is some controversy regarding their rate-determining transition-state structure.

Acknowledgment. Continued financial support by the National Research Council of Canada is gratefully acknowledged.

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Onium Ions. 17.[1a] Improved Preparation, Carbon-13 Nuclear Magnetic Resonance Structural Study, and Nucleophilic Nitrolysis (Nitrative Cleavage) of Diarylhalonium Ions

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Received July 5, 1977

An improved method of preparation of diarylchloronium and diarylbromium ions is described from their corresponding arenediazonium ions by decomposition in haloarenes in the presence of trifluoro- (trichloro-) acetic acid or 2,2,2-trifluoroethyl alcohol. ^{13}C NMR spectroscopic study of the prepared halonium ions shows that nearly equal amounts of charge are transmitted into the two aryl rings regardless of the methyl substitution in one or both rings, suggesting that canonical structures such as I–III are only limited resonance contributors. The potential utility of symmetrical and unsymmetrical diarylchloronium, -bromonium, and -iodonium ions in their nucleophilic nitrolysis with sodium nitrite, giving nitroarenes, was studied. The relative reactivity of the 4-tolyl, phenyl, 3-tolyl, and 2-tolyl salts has been established as 1.0, 3.0, 3.6, and 14.1, respectively. Substitution of tetraphenylborate for hexafluorophosphate as counterion did not affect the product distribution in the nitration reaction. The data reported are best accommodated by an S_N2-like mechanism controlling the collapse of ionic diarylchloronium nitrites, initially formed by displacement of the corresponding counterion, to give nitro- and chlorobenzene derivatives.

Whereas diaryliodonium ions have been extensively studied,[2] only limited data are available on diarylchloronium and -bromonium ions[2] in spite of the high potential utility of these ions as electrophilic arylating agents.[3] This can be attributed to the extremely low yields (0.6–6.6%) obtained in their preparation by Nesmeyanov and co-workers using the decomposition of aryldiazonium tetrafluoroborates in chloro- or bromoarenes.[4–7] Recently Nesmeyanov and co-workers reported an improved preparation of diarylbromium ions by reacting aryllithiums with BrF_3 in 9–28% yields.[8] This method is limited to the preparation of symmetrical diarylbromonium ions. Further difficulties involved in handling BrF_3 and its explosive nature with phenyllithium make the method of little use.

The preparative utility of diarylbrominium tetrafluoroborates was demonstrated by McEwen and Lubinknowski[9a] in their nucleophilic displacement reaction with sodium alkoxides, giving exclusively phenyl alkyl ethers. The corresponding diaryliodonium salts gave under the same conditions, however, aromatic hydrocarbons as the major products[9b] (via a radical path). Reutov and co-workers[9c] carried out the reaction between diarylhalonium salts and triphenylphosphine in light to give (via a radical path) tetraphenylphosphonium ions in 82–92% yields. Nesmeyanov and his co-workers[9d] briefly reported that diarylbromonium and -chloronium ions are quite reactive toward many common nucleophiles, including amines, sodium nitrate, sodium azide, and sodium cyanide. Diphenyliodinium tetrafluoroborate treated with sodium nitrite in aqueous dioxane gave nitrobenzene in 70% yield.[9a] A similar reaction with phenyl-*p*-tolyliodonium tetrafluoroborate yielded a mixture of nitrobenzene and *p*-nitrotoluene in a ratio of 2.5:1.[9d]

A systematic study of the reactivity of diarylchloronium and -brominium ions with nucleophiles, however, has not yet been reported since these halonium salts have been obtained previously only in extremely low yields and were believed to be quite unstable compounds.[10]

Interested in the chemistry of organic halonium ions, we now wish to report an improved method of preparation of diarylchloronium and diarylbrominium ions from their corresponding arenediazonium ions by decomposition in haloarenes in the presence of trifluoro- (trichloro-) acetic acid or 2,2,2-trifluoroethyl alcohol. The developed, improved general method for the preparation of these halonium ions also allowed a systematic study of the nucleophilic nitration of a series of methyl-substituted diarylhalonium salts with sodium nitrite.

Results and Discussion

Preparation of Diarylchloronium and Diarylbromonium Ions. When phenyldiazonium hexafluorophosphate was heated at 60–65 °C in chlorobenzene in the presence of trifluoroacetic acid for 2 h, the reaction mixture subsequently extracted with water, and the aqueous solution neutralized with sodium hydrogen carbonate, the addition of sodium tetraphenylborate caused precipitation of the diphenylchloronium tetraphenylborate salt. The yield of the purified salt recrystallized from acetone–ether was 13%. GC and IR analysis of the organic layer indicated the presence of fluorobenzene (36%), formed in the competitive Schiemenn reaction, and phenyl trifluoroacetate. In addition to trifluoroacetic acid, 2,2,2-trifluoroethyl alcohol, acetic acid, and trichloroacetic acid were also found to be effective; they give the diphenylchloronium salt in 9.0, 4.0, and 8.0% yields, along with fluorobenzene in 40, 51, and 33% yields, respectively. Phenyl 2,2,2-trifluoroethyl ether, phenyl acetate, and phenyl trichloroacetate were formed (based on IR and/or NMR spectroscopy) as the byproducts. Similar arylation failed to take

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0022-3263/78/1943-0463$01.00/0

Table I. Preparation of Diarylhalonium Tetraphenylborates

Diazonium salt	Registry no.	Haloarene	Registry no.		Halonium ion	Registry no.	Mp (dec),[a] °C	Yield[b] from aryldiazonium, % PF_6^-	BF_4^-	$CF_3CO_2^-$
Phenyl	369-58-4	Chlorobenzene	108-90-7	1	Diphenylchloronium	64146-75-4	160–161	13.0	6.6 (3.3)[7]	
Phenyl		Bromobenzene	108-86-1	2	Diphenylbromonium	64146-76-5	172 (166)[c]	8.1	(6.6)[7]	
Phenyl		Iodobenzene	591-50-4	3	Diphenyliodonium	64146-77-5	192 (177)	6.0		
o-Tolyl	19296-22-1	*o*-Chlorotoluene	95-49-8	4	Di-*o*-tolylchloronium	64175-35-5	137–138 (122)	7.6		
m-Tolyl	672-82-2	*m*-Chlorotoluene	108-41-8	5	Di-*m*-tolylchloronium	64146-79-8	138–139	8.9		
p-Tolyl	673-44-9	*p*-Chlorotoluene	106-43-4	6	Di-*p*-tolylchloronium	64146-81-2	136–137	8.6		
o-Tolyl		Chlorobenzene		7	Phenyl-*o*-tolylchloronium	64146-82-3	139 (136)[d]	9.3	5.2 (0.6)[6]	
m-Tolyl		Chlorobenzene		8	Phenyl-*m*-tolyichloronium	64146-84-5	147–148 (136)	9.8	5.0	
p-Tolyl		Chlorobenzene		9	Phenyl-*p*-tolylchloronium	64146-85-6	128 (112)[e]	10.1	5.6 (1.8)[6]	17.1
m-Tolyl		*p*-Chlorotoluene		10	*m*-Tolyl-*p*-tolylchloronium	64146-87-8	141–142 (137)	6.7		
p-Chlorophenyl	1582-27-0	Chlorobenzene		11	Phenyl-*p*-chlorophenylchloronium	64146-88-9	157 (142)	14.0		

[a] Temperatures at which crystals changed are given in parentheses. [b] Yields reported in the literature are given in parentheses. [c] Lit.[4] mp 164–165 °C dec. [d] Lit.[5] mp 160–161 °C. [e] Lit.[6] mp 127 °C dec.

Table II. ^{13}C NMR Chemical Shifts[a,b] for Diarylhalonium Hexafluorophosphates

Ar–X–Ar′	Registry no.	C_1	C_2	C_3	C_4	C_5	C_6	C_1'	C_2'	C_3'	C_4'	C_5'	C_6'	CH_3
1	64146-89-0	139.7	133.6	129.1	134.7	129.1	133.6							
		(134.3)	(124.6)	(129.8)	(126.5)	(129.8)	(124.6)							
2[c]	64146-90-3	133.4		130.9	133.9	130.9								
3	58109-40-3	136.0	114.2	132.7	133.3	132.7	114.2							
4	64146-74-3	138.4[d]	137.9[d]	131.3	135.0	129.3	134.6							
		(134.4)	(135.9)	(130.9)	(127.0)	(126.4)	(129.0)							18.8
5	64146-91-4	139.4	133.1	144.8	135.3	126.0	129.1							
		(134.0)	(129.1)	(139.7)	(127.1)	(129.3)	(125.5)							20.9
6	64146-92-5	136.8	134.0	128.8	146.2	128.8	134.0							
		(131.2)	(128.3)	(130.4)	(136.2)	(130.4)	(128.3)							20.7
7	64146-93-6	139.2	133.6	128.5	135.0	128.5	133.6	138.9	138.4	131.3	135.0	130.3	134.0	18.0
8	64146-94-7	139.6	133.6	129.0	134.7	129.0	133.6	139.4	133.1	144.9	135.4	126.0	129.0	20.8
9	64146-95-8	140.0	133.6	128.9	134.6	128.9	133.6	136.3	134.0	128.9	146.3	128.9	134.0	20.8
10	64146-96-9	139.8	133.1	144.8	135.2	128.9	125.8	136.2	134.0	128.9	146.3	128.9	134.0	20.8, 20.8
11	64146-97-0	139.9	133.7	129.0	134.8	129.0	133.7	137.1	133.4	130.9	140.7	130.9	133.4	

[a] Carbon chemical shifts are relative to external (capillary) Me_4Si. Spectra were recorded in acetone solution at room temperature. [b] Chemical shifts for the corresponding haloarenes[11] are given in parentheses for comparison. [c] Values differ from those previously obtained by Olah et al.[12] for 2 in SO_2 solution at −40 °C. [d] Assignments considered interchangeable.

Table III. Differences between Total ^{13}C Chemical Shifts in Chloroarenes[a] and Diarylchloronium Ions

Diarylhalonium hexafluorophosphates	Ar group		Ar′ group		Total
	Σδ-C	ΔΣδ-C[b]	Σδ-C	ΔΣδ-C[b]	ΔΣδ-C[c]
1	799.8 (777.6)	22.2			44.4
4	806.5 (783.6)	22.9			45.8
5	807.7 (784.7)	23.0			46.0
6	808.6 (784.8)	23.8			47.6
7	808.4 (783.6)	24.8	798.4 (777.6)	20.8	45.6
8	807.8 (784.7)	23.1	799.5 (777.6)	21.9	45.0
9	808.4 (784.8)	23.6	799.6 (777.6)	22.0	45.6
10	807.6 (784.7)	22.9	808.3 (784.8)	23.5	46.4

[a] Total chemical shift values for haloarenes[11] are given in parentheses. [b] $\Delta\Sigma\delta\text{-C} = C_{Ar(\text{or } Ar')\text{ in halonium ion}} - C_{Ar(\text{or } Ar')\text{ in haloarene}}$. [c] $\Delta\Sigma\delta\text{-C} = \Delta\Sigma\delta\text{-}C_{Ar} + \Delta\Sigma\delta\text{-}C_{Ar'}$.

place in the presence of such acids as sulfuric acid, oleum, phosphoric acid, or trifluoromethanesulfonic acid. To change the heterogeneous nature of the reactions to a homogeneous one, acetone or acetronitrile was added as a cosolvent, but the yield of the diphenylchloronium salt decreased. This is attributed to the higher nucleophilic reactivity of these solvents than that of chlorobenzene. In fact, in the presence of acetonitrile, acetanilide[11] was isolated in 55% yield. The yield of diphenylchloronium tetraphenylborate decreased to 6.6% when phenyldiazonium tetrafluoroborate was used instead of the hexafluorophosphate salt. As shown in Table I, aryldiazonium hexafluorophosphates gave consistently better yields than the tetrafluoroborates. In order to prevent the competing formation of fluoroarenes (by the Schiemenn reaction), the counterion was also changed to trifluoroacetate.[12] The yield of phenyl-, *p*-tolyl-, and phenyl-2,4-xylylchloronium tetraphenylborates prepared by this modification increased to 17%.

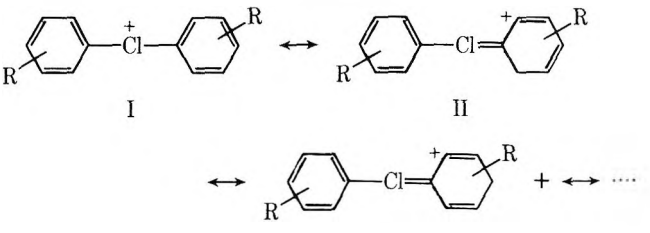
The reaction of phenyldiazonium hexafluorophosphate with bromobenzene and iodobenzene gave diphenylbromonium and iodonium tetraphenylborate in 7.9 and 8.6% yields, respectively.

When aniline itself was reacted with sodium nitrite in trifluoroacetic acid and chlorobenzene in the presence of various dehydrating agents to remove the water generated during diazotization, diphenylchloronium tetraphenylborate was isolated in 6.9, 6.5, 6.0, and 7.0% yields in the case of molecular sieves, anhydrous sodium sulfate, phosphorus pentoxide, and trifluoroacetic anhydride, respectively.

Carbon-13 NMR Spectroscopic Study of Diarylhalonium Ions. The structure of the diarylhalonium salts prepared was subsequently studied by ^{13}C NMR spectroscopy. Diarylchloronium tetraphenylborates displayed complicated ^{13}C NMR spectra since the absorptions of the ring carbons of the anions overlapped with those of the cations. Therefore, the counterion was exchanged for hexafluorophosphate, as described in the Experimental Section. The ^{13}C NMR parameters of the corresponding diarylchloronium hexafluorophosphate salts are summarized in Table II. The assignments were made on the basis of off-resonance spectra, relative intensity of the absorptions, and consideration of molecular symmetry,[13] as well as comparison with the chemical-shift values of the parent haloarenes.[14]

The value of the sum of the ^{13}C NMR chemical shifts of the aryl carbons in each aryl ring is increased by 22 to 24 ppm (Table III) upon transformation of the chloroarenes into diarylchloronium ions, reflecting partial delocalization of the positive charge into the aryl groups.[15] Phenyl and tolyl groups in these ions were shown to possess the similar ability to delocalize the positive charge from the chlorine atom since the aryl carbons undergo an overall deshielding in the ^{13}C NMR spectra of similar magnitude regardless of methyl substitution in one or both aryl rings, the position occupied by the methyl substituent in the tolyl group, or the symmetrical or unsymmetrical nature of the diarylchloronium salt. Thus, a nearly equal amount of charge is transmitted into the two aryl rings.

On the basis of carbon-13 chemical shift data of the diarylchloronium ions studied, it can be concluded that canonical structures such as I–III are only limited resonance contributors[16] as the para carbon resonances when corrected for substituent effects show only extremely small or no differences.



I II

III

Nucleophilic Nitrolysis (Nitrative Cleavage) of Diarylhalonium Salts. In order to study the nucleophilic nitrolysis of diarylhalonium ions as well as symmetrically substituted ions, we also prepared a series of methyl- and halogen-substituted unsymmetrical diarylhalonium tetraphenylborates.

All diarylhalonium tetraphenylborates were prepared by decomposition of the corresponding arenediazonium hexafluorophosphates in haloarenes in the presence of trifluoroacetic acid at 65–70 °C for 2 h, followed by the addition of sodium tetraphenylborate. The data are summarized in Table IV. Phenyl-2-fluorophenylchloronium tetraphenylborate was not obtained by the decomposition of 2-fluorophenyldiazonium hexafluorophosphate in chlorobenzene, but only by the related reaction of phenyldiazonium hexafluorophosphate and 2-chlorofluorobenzene. The structure of the new diarylhalonium salts was ascertained by elemental analysis and NMR spectroscopy.

The reaction of unsymmetrically substituted diarylhalo-

Table IV. Preparation of Methyl- and Halogen-Substituted Unsymmetrical Diarylhalonium Tetraphenylborates from Aryldiazonium Hexafluorophosphates

Diazonium salt	Registry no.	Haloarene		Halonium ion	Registry no.	Mp (dec),[a] °C	Yield, %
m-Tolyl		*o*-Chlorotoluene	12	*o*-Tolyl-*m*-tolylchloronium	64146-99-2	178 (125)	6.5
o-Tolyl		*p*-Chlorotoluene	13	*o*-Tolyl-*p*-tolylchloronium	64147-01-9	140-141	9.0
2,4-Xylyl	64147-33-7	Chlorobenzene	14	Phenyl-2,4-xylylchloronium	64147-03-1	129-130	13.5 (17.0)[b]
		p-Chlorotoluene	15	*p*-Tolyl-2,4-xylylchloronium	64147-14-4	134-135	5.4
		o-Chlorotoluene	16	*o*-Tolyl-2,4-xylylchloronium	64147-16-6	150-152 (142)	4.0
2,3-Xylyl	64147-34-8	Chlorobenzene	17	Phenyl-2,3-xylylchloronium	64147-18-8	115-117 (106)	9.3
		o-Chlorotoluene	18	*o*-Tolyl-2,3-xylylchloronium	64147-20-2	126-127 (114)	5.4
Phenyl		*o*-Chlorofluorobenzene	19	Phenyl-*p*-fluorophenylchloronium	64147-22-4	144-146 (136)	2.5
		m-Chlorofluorobenzene	20	Phenyl-*m*-fluorophenylchloronium	64147-24-6	151-152 (132)	2.4
		o-Dichlorobenzene	21	Phenyl-*o*-chlorophenylchloronium	64147-26-8	152-153 (145)	7.3
o-Tolyl		Bromobenzene	22	Phenyl-*o*-tolylbromonium	64147-28-0	164-165 (144)	11.6
p-Tolyl		Bromobenzene	23	Phenyl-*p*-tolylbromonium	64147-29-1	141.2 (139)[c]	9.7
o-Tolyl		Iodobenzene	24	Phenyl-*o*-tolyliodonium	64147-31-5	153-154 (132)	5.7
p-Tolyl		Iodobenzene	25	Phenyl-*p*-tolyliodonium	64147-32-6	112-113 (105)	5.7

[a] Temperatures at which crystals started to change are given in parentheses. [b] Yield was obtained for 2,4-xylyldiazonium trifluoroacetate. [c] Lit.[8] mp 135 °C dec.

nium tetraphenylborates with nitrite ion gives, in a nucleophilic nitrolysis reaction, a mixture of the corresponding nitroarenes (eq 1). The nitroarene product composition reflects the effect of the substituents on the course of the nucleophilic nitrolysis.

$$\mathrm{Ar{-}X^{+}{-}Ar\ BPh_4^-} \xrightarrow{\mathrm{NaNO_2}} \mathrm{ArNO_2 + Ar'NO_2} + \mathrm{ArX + ArX'} \quad (1)$$

To carry out the nucleophilic nitration, equimolecular amounts of the diarylhalonium salts and sodium nitrite were refluxed in a mixture of acetone–water (5:1 v/v) in the presence of benzonitrile as an internal standard for subsequent GC analysis of the reaction products. In the case of the phenyl-4-tolyliodonium salt, 2-nitrotoluene was substituted for benzonitrile since the latter and 4-iodotoluene gave overlapping GC peaks under the experimental conditions.

On the basis of a ^{13}C NMR spectroscopic study of diarylhalonium ions, the effect of the halonium center is mostly reflected in its inductive effect on the aryl rings. As expected from the greater electronegativity of chlorine and bromine relative to iodine, diarylchloronium and -bromonium ions were found to be more reactive than the corresponding diaryliodonium ions. In fact, when diphenylchloronium or diphenylbromonium salts were reacted with sodium nitrite under similar conditions, the reactions were completed within 2 h to give nitrobenzene in 75% yield, whereas 65% of the starting diphenyliodonium salt was recovered unreacted under the same conditions.

Nitration of 2,2′-, 3,3′-, and 4,4′-ditolylchloronium tetraphenylborate gave 2-, 3-, and 4-nitrotoluene, respectively. Not even trace amounts of other isomers were detected, showing that only ipso attack occurred. This rules out the possible formation of a benzene intermediate or attack at other ring positions, which would be the case if the diarylhalonium ions would show ambident character.

In the nucleophilic substitution reactions of 4-substituted diaryliodonium salts, nucleophiles generally attack the phenyl ring carrying electron-withdrawing groups.[17] This trend is also observed in the nucleophilic nitration of phenyl-4-tolylchloronium hexafluorophosphate, where the obtained nitrobenzene to 4-nitrotoluene ratio is 3.0:1.0. Nitration of phenyl-3-tolylchloronium hexafluorophosphate gave a mixture of nitrobenzene and nitrotoluene in a ratio of 1.0:1.2, indicating the weak effect of 3-methyl relative to 4-methyl substitution in the course of the reaction. On the other hand, 2-methyl substitution of one of the aryl rings was shown to exert the opposite effect on the relative reactivity of the rings. 2-Nitrotoluene was formed 4.7 times faster than nitrobenzene in the nitration of phenyl-2-tolylchloronium hexafluorophosphate. Similar effects were reported in the related pyrolysis[18a,b] and hydrolysis.

The charge density in the phenyl ring in the series of diphenylchloronium and phenyltolylchloronium hexafluorophosphates has been shown, based on the discussed ^{13}C NMR studies, to be similar, i.e., independent of the nature of the second aryl group (phenyl, *o*-, *m*-, or *p*-tolyl). A relative scale of reactivities can be established for these groups toward nucleophilic nitration assuming that the reactivity of the unsubstituted phenyl ring is predominantly controlled by its charge density (affected mainly by the inductive effect of the halonium center) and hence remains relatively constant along the series of related halonium ions. In this manner, the relative reactivity of the 4-tolyl, phenyl, 3-tolyl, and 2-tolyl rings toward nitrite ion can be established as 1.0, 3.0, 3.6, and 14.1, respectively, on the basis of the nitrobenzene to nitrotoluene product ratio formed in the nitration of phenyltolylchloronium salts. Excellent agreement was obtained in the nucleophilic nitration of unsymmetrical ditolylchloronium salts

Table V. Ratio of Nitroarenes in the Reaction $Ar\text{-}\overset{+}{X}\text{-}Ar' \cdot BPh_4^- \xrightarrow{NaNO_2} ArNO_2 + Ar'NO_2 + ArX + Ar'X$

Halonium ion ($Ar\text{-}\overset{+}{X}\text{-}Ar'$)	Products		$ArNO_2/Ar'NO_2$ Ratio	
	$ArNO_2$	$Ar'NO_2$	Obsd	Calcd
$2\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}Ph$	2-Nitrotoluene	Nitrobenzene	4.7:1.0	
$3\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}Ph$	3-Nitrotoluene	Nitrobenzene	1.2:1.0	
$4\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}Ph$	4-Nitrotoluene	Nitrobenzene	1.0:3.0	
$2\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}3'\text{-}CH_3C_6H_4$	2-Nitrotoluene	3-Nitrotoluene	3.9:1.0	3.9:1.0
$2\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}4'\text{-}CH_3C_6H_4$	2-Nitrotoluene	4-Nitrotoluene	13.5:1.0	14.1:1.0
$3\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}4'\text{-}CH_3C_6H_4$	3-Nitrotoluene	4-Nitrotoluene	3.4:1.0	3.6:1.0
$2,4\text{-}(CH_3)_2C_6H_3\text{-}\overset{+}{I}\text{-}Ph$	4-Nitro-*m*-xylene	Nitrobenzene	1.8:1.0	1.6:1.0
$2,4\text{-}(CH_3)_2C_6H_3\text{-}\overset{+}{I}\text{-}4'\text{-}CH_3C_6H_4$	4-Nitro-*m*-xylene	4-Nitrotoluene	3.7:1.0	4.7:1.0
$2,4\text{-}(CH_3)_2C_6H_3\text{-}\overset{+}{I}\text{-}2'\text{-}CH_3C_6H_4$	4-Nitro-*m*-xylene	2-Nitrotoluene	1.0:1.7	1.0:3.0
$2,3\text{-}(CH_3)_2C_6H_3\text{-}\overset{+}{I}\text{-}Ph$	3-Nitro-*o*-xylene	Nitrobenzene	11.0:1.0	5.6:1.0
$2,3\text{-}(CH_3)_2C_6H_3\text{-}\overset{+}{I}\text{-}2'\text{-}CH_3C_6H_4$	3-Nitro-*o*-xylene	2-Nitrotoluene	1.9:1.0	1.2:1.0
$2\text{-}FC_6H_4\text{-}\overset{+}{I}\text{-}Ph$	2-Nitrofluorobenzene	Nitrobenzene	1.0:4.5	
$3\text{-}FC_6H_4\text{-}\overset{+}{I}\text{-}Ph$	3-Nitrofluorobenzene	Nitrobenzene	1.3:1.0	
$2\text{-}ClC_6H_4\text{-}\overset{+}{I}\text{-}Ph$	2-Nitrochlorobenzene	Nitrobenzene	1.8:1.0	
$4\text{-}ClC_6H_4\text{-}\overset{+}{I}\text{-}Ph$	4-Nitrochlorobenzene	Nitrobenzene	1.0:2.0	
$2\text{-}CH_3C_6H_4\text{-}\overset{+}{Br}\text{-}Ph$	2-Nitrotoluene	Nitrobenzene	7.6:1.0	
$4\text{-}CH_3C_6H_4\text{-}\overset{+}{Br}\text{-}Ph$	4-Nitrotoluene	Nitrobenzene	1.0:3.1	
$2\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}Ph$	2-Nitrotoluene	Nitrobenzene	9.6:1.0	
$4\text{-}CH_3C_6H_4\text{-}\overset{+}{I}\text{-}Ph$	4-Nitrotoluene	Nitrobenzene	1.0:2.7	

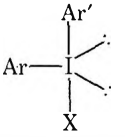
between the observed product distributions and those calculated from the relative reactivity values for the phenyl and tolyl rings, respectively (Table V). Less satisfactory correlation was, however, observed in the case of phenyl- and tolylxylylchloronium salts.

Nearly identical product distributions were obtained in the nitration of phenyl-4-tolylchloronium, -bromonium, and -iodonium salts. However, the *o*-methyl substituent effect increased in the sequence phenyl-2-tolylchloronium < -bromonium < -iodonium ions. The amount of 2-nitrotoluene obtained from the iodonium ion was approximately twice as much as that obtained from the chloronium ion. Nitration of phenyl-2,6-xylylchloronium, -bromonium, and -iodonium ions gave 2-nitro-*m*-xylene and the corresponding haloarene almost exclusively, indicating the reinforced ortho effect. The effect of the chloronium center upon the relative reactivity of the phenyl and the chlorophenyl rings in the nitration of phenyl-4-chlorophenyl- and phenyl-2-chlorophenylchloronium ions was shown to be smaller than that observed in the case of methyl substitution, although attack by the nitrite ion took place in the same direction. However, in the case of the phenyl-2-fluorophenylchloronium ion, a reversed ortho effect was observed; the 2-nitrofluorobenzene to nitrobenzene ratio was 1.0:4.5.

Substitution of tetraphenylborate for hexafluorophosphate as counterion did not affect the product distribution in the nitration of phenyl-2-tolyl- and phenyl-4-tolylchloronium salts. These results suggest that the counterion has no particular effect on the reactions.

In the studied reactions, nitroarenes were obtained in 70–75% yield, and only relatively small amounts of phenols (<8%) and biphenyls (<10%) were detected. The presence of water in the reaction media as well as the ambident nature of the nitrite ion can account for the formation of phenols. Since biphenyl was detected even from ditolylchloronium tetraphenylborate, but in substantially decreased yield (~2%) in the case of diphenylchloronium hexafluorophosphate, it must be mostly formed from the tetraphenylborate anion and not as a reaction byproduct from the diarylhalonium ion. In the nitration of phenyl-4-tolylchloronium and 3,3′-ditolylchloronium tetraphenylborate, a small amount of toluene and trace amounts of 4-tolylbenzene and 3,3′-dimethylbiphenyl, respectively, were detected by GC. These results indicate that radical side reactions take place only to a minor degree.

Yamada and Okawara[18a] reported in the pyrolysis of diaryliodonium bromides that the predominant attack of the bromide ion was on the *o*-methyl-substituted aryl ring, proposing a methyl-substituted phenyl cation intermediate. Wiegand and co-workers[18b] observed a similar ortho effect in the pyrolysis of a series of phenylaryliodonium chlorides, bromides, and iodides-131, suggesting the formation of a tricovalent iodine intermediate with subsequent S_N-like displacement leading to products. Since only the equatorial aryl ring is capable of reacting with the halide ion (X^-) and the bulkier ortho-substituted aryl ring (Ar) should be expected



to preferentially occupy the equatorial position, the observed ortho effect[18b] was satisfactorily explained for diaryliodonium halides.

Although this mechanisms involving a tricovalent iodide intermediate could be applied in the case of nitration of the phenyl-2-tolyliodonium salt, it should not be applicable to the nitration of diarylchloronium salts since the formation of the corresponding tricovalent chlorine intermediate represents a much more unlikely path because of the inherently lesser ability of chlorine relative to the iodine to form such tricovalent compounds.[6] The bond between chloronium ions and their counterion in diarylchloronium salts must be considered to be mostly ionic. Furthermore, a mechanism involving a phenyl cation intermediate is less probable, at least for the nitration reaction under our experimental conditions, since in this case phenols would be expected to be also inevitably formed in aqueous acetone media, which was not the case.

The data reported herein for the nucleophilic nitration of diarylchloronium salts are best accommodated by a S_N2-like mechanism controlling the collapse of ionic diarylchloronium nitrites initially formed by displacement of the corresponding counterion (tetraphenylborate or hexafluorophosphate) to give nitro- and chlorobenzene derivatives. The nitrite ion attacks the most activated (by the negative inductive effect) ipso carbon position. *p*-Methyl substitution relative to the ipso carbon (C_1) decreases the latter's charge density, and hence it deactivates C_1 to undergo nucleophilic attack, in comparison to the ipso carbon (C_1') in the unsubstituted phenyl ring.

m-Methyl substitution hardly affects the reactivity of the ipso carbon (C_1'), which is in good agreement with expectations on the basis of the proposed S_N2 mechanism.[20] In the case of the *o*-methyl-substituted diarylchloronium ions, steric strain due to the ortho substituent (s) will be operative and weakens the carbon–chlorine bond, thus activating the ipso carbon (C_1) in the ortho-substituted aryl ring. Results show that the steric ortho effect is much more important than the deactivating effect due to the electron-donor character of the methyl group. Similarly to the case of unsymmetrical ditolylchloronium salts, good agreement between the observed and the calculated product distributions was obtained in the nitration of phenyl-, 4-xylyl-, 4′-tolyl-2,4-xylyl-, and especially phenyl-2,3-xylylchloronium salts, where additional steric factors are introduced in the latter case. Larger than expected amounts of 3-nitro-*o*-xylene were found; i.e., the 2,3-xylyl group was found to be more reactive than the 2-tolyl group in nucleophilic nitration of the corresponding chloronium salts.

The remarkable decrease of the ortho effect in phenyl-2-chlorophenyl- and phenyl-2-fluorophenylchloronium salts can be accounted for by the mesomeric effect of the halogen atom and the electrostatic repulsion between the nitrite ion and the halogen substituent.

Experimental Section

General. All melting points reported in Table I are uncorrected and were measured on a Fischer-Johns melting point apparatus.

Carbon-13 NMR spectra were obtained using a Varian Model XL 100 spectrometer equipped with a broad-band decoupler and a Fourier transform accessory. It was operated in the pulse Fourier transform mode, employing typically 3000–5000 (5) μs pulses in order to obtain a satisfactory signal to noise ratio.

Materials. Aryldiazonium hexafluorophosphates were synthesized according to a procedure of Rutherford et al.[21]

Diphenylchloronium Tetraphenylborate. Preparation from Phenyldiazonium Hexafluorophosphate. A well-stirred heterogenous mixture of phenyldiazonium hexafluorophosphate (2.5 g, 10 mmol), trifluoroacetic acid (3 mL), and chlorobenzene (10 mL) was heated at 65–70 °C for 2 h, during which time the evolution of nitrogen gas was completed. After addition of ethyl ether and petroleum ether (1:1, 20 mL), the reaction mixture was extracted with water (15 mL × 3). The aqueous phase was neutralized by sodium hydrogen carbonate. Addition of sodium tetraphenylborate (~2 mmol) produced a white precipitate, which was collected and washed with water. The precipitate was dissolved in hot acetone, and the small amount of insoluble material was filtered off. The acetone was evaporated under reduced pressure, and the residual solid was redissolved in hot acetone. Addition of ethyl ether precipitated crystals of the salt (0.66 g, 13%); mp 160–160.5 °C (lit.[7] 160–161 °C).

The other diarylhalonium tetraphenylborates listed in Table I were prepared from the corresponding aryldiazonium hexafluorophosphates (or tetrafluoroborates) and haloarenes in the same manner as described above.

Preparation from Aniline. To a mixture of aniline (930 mg, 10 mmol), sodium sulfate (1.42 g, 10 mmol), and chlorobenzene (10 mL) trifluoroacetic acid (4 mL) was added. The mixture was cooled in an ice bath, and sodium nitrite (690 mg, 11 mmol) was slowly added with stirring. The mixture was stirred for 1 h at 10 °C and then heated at 60 °C for 2 h. The same workup described above gave 0.339 g (6.5%) of the product.

Diarylhalonium Hexafluorophosphates. To a suspension of the corresponding diarylhalonium tetraphenylborate (0.4 mmol) in ethyl ether (4 mL) 40% hexafluorophosphoric acid (0.5 mL) was added with stirring at room temperature. The reaction was exothermic, and before complete dissolution of the starting material the corresponding diarylhalonium hexafluorophosphate precipitated. After 1.5 h, ethyl ether/*n*-pentane (1:7 v/v) was added, and the salt was filtered and washed with the ethyl ether/pentane mixture; yield 70–80%. ^{13}C NMR spectra of these salts were recorded without further purification.

All diarylhalonium salts gave correct elemental analyses (Galbraith Laboratories Inc.).

Nitration of Diarylchloronium Salts. Diarylchloronium tetraphenylborate or hexafluorophosphate (0.1 mmol), sodium nitrite (10 mg), and benzonitrile (10 mg, as an internal standard for GC) in acetone (2.5 mL)–water (0.5 mL) were refluxed for 2 h. After the addition of ethyl ether–*n*-pentane (1:1 v/v), an aqueous layer was separated. The organic layer was washed with diluted aqueous sodium chloride. The combined aqueous layer was extracted with ethyl ether–*n*-pentane, and the combined organic layer was dried over sodium sulfate. The solvents were distilled out at atmospheric pressure below 60 °C, and after the addition of a small amount of acetone the residue was analyzed by GC. When the phenol generated interfered with the integration of the peak of the nitro compound, the organic layer was washed with 5% aqueous sodium hydroxide.

Nitration of Diarylbromonium Salts. Diarylbromonium tetraphenylborate (0.1 mmol), sodium nitrite (10 mg), and benzonitrile (10 mg) in dioxane (2.5 mL)–water (0.5 mL) were refluxed for 1 day. The reaction mixture was treated similarly as described above and analyzed by GC.

Nitration of Diaryliodonium Salts. Diaryliodonium tetraphenylborate (0.1 mmol), sodium nitrite (10 mg), and benzonitrile (10 mg) in dioxane (4 mL)–water (1 mL) were refluxed for 2 days. The reaction mixture was worked up as described above and analyzed by GC.

Gas chromatographic analyses of the reaction products were performed on a Perkin-Elmer Model 226 gas chromatograph equipped with a hydrogen flame ionization detector and open tubular capillary columns. Peak areas were obtained with a Columbia Scientific Industries Model CSI-208E printing integrator. A 150 ft × 0.01 in capillary column coated with butanediol succinate was used for the analyses of nitrobiphenyl and -phenol derivatives at a standard temperature of 160 °C and a helium flow rate of 20 psi. Biphenyl and phenol derivatives were analyzed similarly except for using a 100-ft long column at 140 °C and a helium flow rate of 20 psi. Toluene was detected by using a 150 ft × 0.01 in capillary column coated with *m*-bis(*m*-phenoxyphenoxy)benzene and Apiezon L.

Acknowledgment. The support of our work by the U.S. Army Research Office is gratefully acknowledged.

Registry No.—Sodium tetraphenylborate, 143-66-8; aniline, 62-53-3; hexafluorophosphoric acid, 16940-81-1; sodium nitrite, 7632-00-0.

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Synthesis of Fervenulin 4-Oxide and Its Conversion to the Antibiotics Fervenulin and 2-Methylfervenulone[1]

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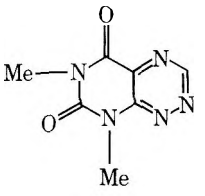
Received July 15, 1977

Normally inaccessible fervenulin 4-oxide (**5**) was synthesized in a single step by the reaction of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (**4**) with one-carbon reagents (dimethylformamide–phosphorus oxychloride, dimethylformamide–dimethyl sulfate, formic acid, and triethyl orthoformate). Compound **5** was found to be a versatile intermediate for the synthesis of antibiotics fervenulin (**1**) and 2-methylfervenulone (MSD-92) (**2**). Namely, the antibiotic **1** could be synthesized in the highest yield when **5** was treated with sodium hydrosulfite in water. The antibiotic **2** was synthesized most conveniently by the following three steps: treatment of **5** with dimethylformamide–phosphorus oxychloride afforded 3-chloro-6,8-dimethylpyrimido[5,4-e]-*as*-triazine-5,7(6*H*,8*H*)-dione (**14**), followed by acid hydrolysis to fervenulone (**15**), and subsequent alkylation with methyl iodide in dimethylformamide containing potassium carbonate. Some derivatives related to **1** or **5** were also prepared from **4** or **5**.

In recent years considerable chemical and medicinal interest has been focused on the pyrimido[5,4-*e*]-*as*-triazine (7-azapteridine) ring system primarily because of the attractive biological activities displayed by the antibiotics fervenulin (**1**), 2-methylfervenulone (MSD-92) (**2**), and toxoflavin (**3**).[2] In connection with our recent studies on the synthesis of purines[3] and pteridines[4] from 6-amino-1,3-dimethyl-5-nitrosouracil, we have now examined the reaction of readily available 1,3-dimethyl-6-hydrazino-5-nitrosouracil (**4**)[5] with various one-carbon reagents (dimethylformamide–phosphorus oxychloride, dimethylformamide–dimethyl sulfate,[6] formic acid, and triethyl orthoformate) and have found that the respective product is surprisingly fervenulin 4-oxide (**5**), which is a versatile intermediate for the synthesis of pyrimido[5,4-*e*]-*as*-triazine derivatives including the antibiotics **1** and **2**.



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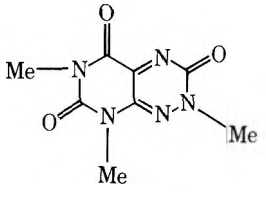

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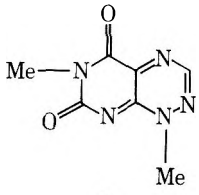

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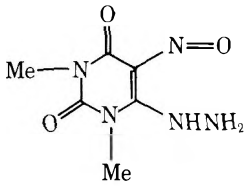

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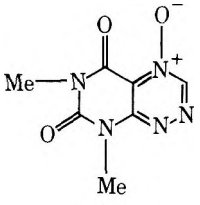

5

The 4-oxide **5** seems to be less accessible by the conventional peroxy acid oxidation since the π-electron distribution of **1** calculated by the Hückel LCAO–MO method indicates that the most reactive site for the oxidation is position 1.[7] In fact, the oxidation of **1** with trifluoroperacetic acid has been shown to give fervenulin 1-oxide.[8] Recently, Yoneda et al.[7] reported the synthesis of 3-substituted fervenulin 4-oxides by the nitrosative cyclization of 6-alkylidene(or benzylidene)hydrazino-1,3-dimethyluracils in the presence of diethyl azodicarboxylate. However, the preparation of **5** itself has not been described. We now wish to report four new one-step syntheses of **5** and its successful conversion to the antibiotics **1** and **2** as well as to some derivatives related to **1**.

Fervenulin 4-Oxide. Treatment of **4** with a mixture of dimethylformamide and phosphorus oxychloride (Vilsmeier reagent) at 0 °C followed by stirring at room temperature for 30 min gave **5** in 72% yield (method A). The structure of **5** was assigned by the satisfactory elemental analysis and spectral data. The mass spectrum showed a strong parent ion at *m/e* 209 and a remarkable $M^+ - 16$ ion due to the presence of *N*-oxide. The NMR spectrum revealed the presence of two *N*-methyl groups (δ 3.45 and 3.80) and a single aromatic proton (δ 10.30). The structure of **5** was finally corroborated by its successful reduction to the antibiotic **1** (vide infra). The formation of **5** presumably proceeds through the *N,N*-dimethylaminomethylenehydrazino intermediate **6**, followed by cyclization, and subsequent aromatization by loss of dimethylamine.[9] There seem to be no previous instances in which the Vilsmeier reagent has been used for the synthesis of heterocyclic *N*-oxides. Method A was found to be greatly dependent on the reaction temperature. When this reaction was attempted without cooling, the product obtained was not **5** but *v*-triazolo[4,5-*d*]pyrimidine derivatives (**9**),[10] which arise from the intramolecular dehydrative cyclization of **4**. In analogy with method A, treatment of **4** with dimethylformamide–dimethyl sulfate complex[6] (a modified Vilsmeier reagent) at room temperature for 2 h afforded a 43% yield of **5**, probably via the same intermediate with that of method A (method B). Refluxing **4** with formic acid for 30 min also provided a 54% yield of **5**, presumably formed via the dehydrative cyclization of a formylhydrazino intermediate **7** (method C). Furthermore, heating **4** with triethyl orthoformate at 90 °C for 30 min caused the separation of **5** in 71% yield (method D). This method appears to have greater scope than those of methods A, B, and C, and constitutes a general synthetic route to fervenulin 4-oxide derivatives. For example, the reaction of **4** with triethyl orthoacetate or triethyl orthopropionate under the conditions described above furnished the corresponding 3-alkylfervenulin 4-oxides, **10**[7] and **11**, in high yields. The condensation of **4** with ortho esters may be involved with the intermediacy of α-ethoxyalkylidenehydrazino derivative **8**, which undergoes cyclization by the elimination of ethanol. In general, the proposed intermediates, **6**, **7**, and **8**, described in the above reactions can exist in either nitroso or oxime forms; however, these cyclizations may be facilitated by the nucleophilicity of the latter. The partici-

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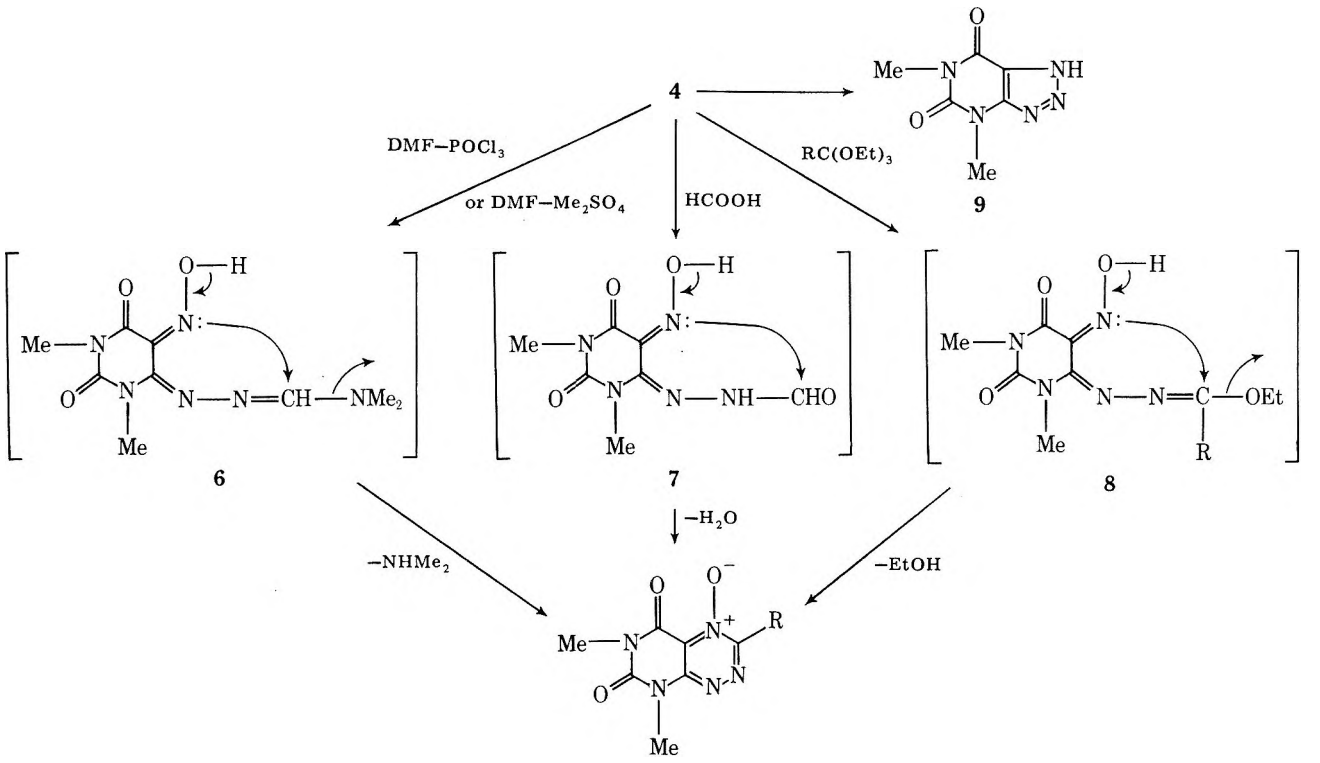
Scheme I



pation of oxime groups as nucleophiles has been well documented[11] (Scheme I).

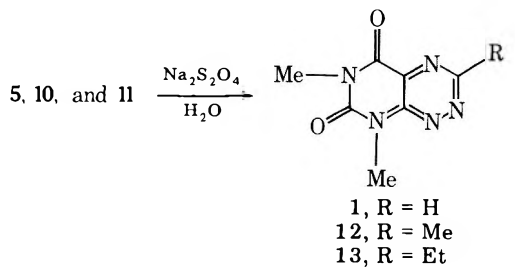
Fervenulin and 2-Methylfervenulone. The total syntheses of antibiotics fervenulin (**1**)[5,8,12–16] and 2-methylfervenulone (MSD-92) (**2**)[15] have been accomplished. We have now examined a new synthetic approach to these antibiotics starting with fervenulin 4-oxide (**5**) obtained above.

Antibiotic **1** could be obtained in an excellent yield by the reduction of **5** with aqueous sodium hydrosulfite at room temperature. Compound **1** thus obtained was identical in all respects with the authentic sample prepared by the reported procedure.[5] Analogously, compounds **10** and **11** were converted to the corresponding 3-alkylfervenulins, **12** and **13**. The deoxygenation of *N*-oxide function of **5** to **1** was also achieved by the prolonged heating with dimethylformamide in less satisfactory yield (Scheme II).

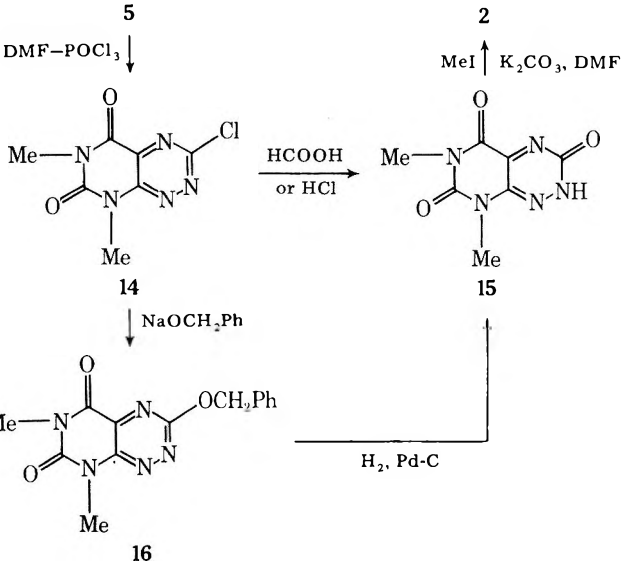
Antibiotic **2** was prepared most conveniently by three steps starting with **5** as described below. Treatment of **5** with a mixture of dimethylformamide and phosphorus oxychloride at 50 °C afforded the chloro derivative **14**[15] in 84% yield. Heating **14** with either formic acid[17] at reflux or 2 N hydrochloric acid at 90 °C gave fervenulone (**15**),[15] the precursor of **2**, in 89 and 51% yield, respectively. Compound **15** could also be obtained from **14** by the indirect route. Thus the nucleophilic displacement of chloride from **14** with sodium benzyloxide gave the benzyloxy derivative **16**, and the subsequent removal of the benzyl group by catalytic reduction with palladium charcoal provided **15** in 50% yield. The final alkylation was accomplished in almost quantitative yield by the reaction of **15** with methyl iodide in dimethylformamide containing potassium carbonate. The spectral data (IR, NMR, MS, and UV) of the synthetic compound and those of the authentic sample described in the literature[18] proved to be identical (Scheme III).

In connection with **15**, we also attempted the direct synthesis of **15** from **5** since various heterocyclic *N*-oxides have been known to react with nucleophiles to give α-hydroxy compounds.[19] However, these attempts were found to be unsuccessful. Thus, treatment of **5** with tosyl chloride in

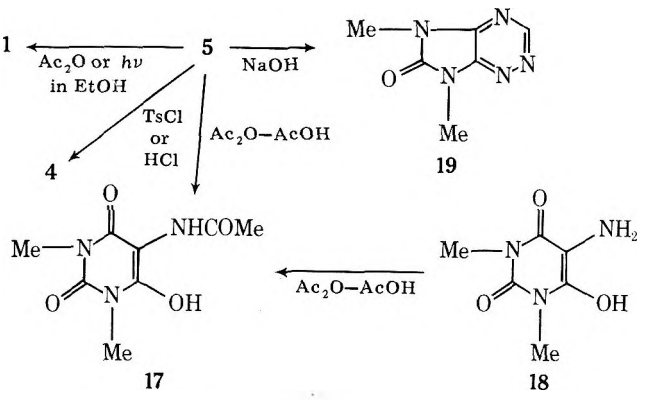
Scheme II



Scheme III



Scheme IV



chloroform caused the ring cleavage of the *as*-triazine nucleus to give the starting material (**4**), which was alternatively obtained by the action of methanolic hydrochloric acid on **5**. Refluxing **5** with acetic anhydride gave only **1**. Treatment of **5** with a mixture of acetic anhydride and acetic acid furnished 5-acetylamino-1,3-dimethylbarbituric acid (**17**), which was identical with the sample prepared by the acetylation of 5-amino-1,3-dimethylbarbituric acid (**18**)[20] with a mixture of acetic anhydride and acetic acid.[21] In contrast to the acids, treatment of **5** with 0.5% sodium hydroxide resulted in the deoxygenation of the *N*-oxide group and ring contraction of the pyrimidine moiety to give a new class of azapurine, imidazo[4,5-*e*]-*as*-triazine derivative (**19**), in 40% yield.[22] The structure of **19** was supported by the elemental analysis and spectral data. In particular the IR spectrum revealed a characteristic carbonyl band at 1750 cm^{-1},[23] and the NMR spectrum showed the presence of two *N*-methyl groups (δ 3.31 and 3.40) and a single aromatic proton (δ 10.23). The mechanism of this ring contraction probably involves a benzylic acid type rearrangement which has been discussed in the conversion of a certain pyrimido[5,4-*g*]pteridine 5-oxide to an imidazo[4,5-*b*]pyrazine by the action of sodium hydroxide.[24] The photoirradiation of **5** in ethanol provided only **1** in 54% yield and no rearrangement of the *N*-oxide group was observed (Scheme IV).

Experimental Section

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Japan Spectroscopic Co., Ltd. Model IR-E spectrophotometer from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. UV spectra were recorded on a Hitachi 124 spectrophotometer. Mass spectra were performed on a JMS D100 EI spectrometer by a direct inlet system at 75 eV.

6,8-Dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-Oxide (Fervenulin 4-Oxide (5)). Method A. The suspension of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (**4**)[5] (0.199 g, 0.001 mol) in dry DMF (3 mL) was stirred at 0 °C while the Vilsmeier reagent prepared from dry DMF (0.29 g, 0.004 mol) and $POCl_3$ (0.153 g, 0.001 mol) was added dropwise. When the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The resulting solution was diluted with EtOH (2 mL) and evaporated in vacuo. The residue was poured onto ice–water and the precipitated solid was filtered. Recrystallization from EtOH gave **5** (0.15 g, 72%): mp 179—180 °C; IR 1715, 1660 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.45 (s, 3 H, NCH_3), 3.80 (s, 3 H, NCH_3), 10.30 (s, 1 H, C^3H); UV λ_{max} (EtOH) 240 nm (log ϵ 4.10), 304 (3.21), 323 sh (2.78); MS *m/e* 209 (M^+), 193 ($M^+ - 16$).

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 39.92; H, 3.41; N, 33.76.

When this reaction was carried out without cooling, 4,6-dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**9**) (0.1 g, 55%), mp 259—260 °C (lit.[10] mp 260 °C), identical (IR) with an authentic sample,[10] was obtained after evaporation of the reaction mixture, followed by recrystallization of the residue from H_2O.

Method B. A mixture of **4** (0.199 g, 0.001 mol) and dimethylformamide–dimethyl sulfate complex[6] (0.6 g, 0.003 mol) was stirred at room temperature for 2 h. The resulting solution was diluted with EtOH (1 mL) and the precipitates were filtered. Recrystallization from EtOH afforded **5** (0.09 g, 43%), mp 179—180 °C, identical with a sample of **5** prepared by method A.

Method C. A mixture of **4** (0.199 g, 0.001 mol) and HCOOH (3 mL) was refluxed for 30 min and the reaction mixture was evaporated in vacuo. The residue was recrystallized from EtOH to give **5** (0.11 g, 54%), mp 179—180 °C, identical in all respects with the material prepared as described above.

Method D. A suspension of **4** (0.199 g, 0.001 mol) in triethyl orthoformate (3 mL) was heated at 90 °C for 30 min. After cooling the reaction mixture, the precipitated solid was filtered and recrystallized from EtOH to give **5** (0.148 g, 71%), mp 179–180 °C, identical with the material prepared by methods A, B, and C.

3-Alkyl-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-Oxides (3-Alkylfervenulin 4-Oxides (10 and 11)). General Procedure. A mixture of **4** (0.199 g, 0.001 mol) and the respective ortho esters (2 mL) was heated for 30 min at 90 °C. The resulting solution was evaporated in vacuo and the residue was recrystallized from an appropriate solvent to give the corresponding fervenulin 4-oxides (**10** and **11**).

Compound **10:** recrystallized from EtOH (0.17 g, 76%); mp 137–138 °C (lit.[7] mp 138 °C); IR 1715, 1660 cm^{-1} (CO); MS *m/e* 223 (M^+), 207 ($M^+ - 16$). Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.06; H, 4.06; N, 31.65.

Compound **11:** recrystallized from EtOAc (0.2 g, 85%); mp 145.5–147 °C; IR 1725, 1670 cm^{-1} (CO); MS *m/e* 237 (M^+), 221 ($M^+ - 16$). Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.22; H, 4.62; N, 29.27.

6,8-Dimethylpyrimido[5,4-e]-*as*-triazine-5,7(6*H*,8*H*)-dione (Fervenulin (1)). Method A. A mixture of **5** (0.209 g, 0.001 mol) and $Na_2S_2O_4$ (0.522 g, 0.003 mol) in H_2O (3 mL) was stirred at room temperature for 1 h. The resulting clear solution was extracted with $CHCl_3$ (three 5-mL portions). The $CHCl_3$ extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from C_6H_6 to give **1** (0.17 g, 90%): mp 177–178 °C (lit.[5] mp 178–179 °C); IR 1725, 1670 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.60 (s, 3 H, NCH_3), 3.93 (s, 3 H, NCH_3), 9.47 (s, 1 H, C^3H); UV λ_{max} (EtOH) 237 nm (log ϵ 3.97), 275 sh (2.99), 343 (3.16); MS *m/e* 193 (M^+).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.65; N, 36.26. Found: C, 43.33; H, 3.61; N, 36.19.

Method B. A mixture of **5** (0.104 g, 0.0005 mol) in dry DMF (3 mL) was refluxed for 8 h and the reaction mixture was concentrated in vacuo. The residue was recrystallized from C_6H_6 to give **1** (0.06 g, 60%), mp 177–178 °C, identical with a sample of **1** prepared by method A. Treatment of **5** (0 104 g, 0.0005 mol) with Ac_2O (3 mL) under the same conditions afforded **1** (0.02 g, 21%).

Method C. A solution of **5** (0.209 g, 0.001 mol) in EtOH (400 mL) was irradiated with a 100-W high-pressure mercury lamp surrounded by a water-cooled Pyrex filter at room temperature for 20 min. The reaction mixture was evaporated in vacuo and the residue was recrystallized from C_6H_6 to afford **1** (0.104 g, 54%), mp 177–178 °C, identical with the material prepared by methods A and B.

3-Alkyl-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7-(6*H*,8*H*)-diones (3-Alkylfervenulins (12 and 13)). General Procedure. A mixture of **10** or **11** (0.001 mol) and $Na_2S_2O_4$ (0.522 g, 0.003 mol) in H_2O (3 mL) was treated as described in method A of **1**.

Compound **12:** recrystallized from *n*-hexane (0.176 g, 85%), mp 112–113 °C (lit.[8] mp 127 °C); IR 1725, 1670 cm^{-1} (CO); MS *m/e* 207 (M^+). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.69; H, 4.46; N, 34.15.

Compound **13:** recrystallized from *n*-hexane (0.12 g, 55%), mp 88–89 °C; IR 1730, 1685 cm^{-1} (CO); MS *m/e* 221 (M^+). Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.55; H, 4.93; N, 31.64.

3-Chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (14). A mixture of **5** (0.209 g, 0.001 mol) and $POCl_3$ (0.6 mL) in dry DMF (3 mL) was stirred at 50 °C for 2 h. The reaction mixture was evaporated in vacuo and the residue was covered with ice–water. The precipitates were filtered and recrystallized from EtOH to yield **14** (0.19 g, 84%), mp 147 °C (lit.[15] mp 146–147 °C); IR 1740, 1675 cm^{-1} (CO); MS *m/e* 227 (M^+), 229 ($M^+ + 2$).

Anal. Calcd for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.66; N, 30.77. Found: C, 37.06; H, 2.72; N, 30.98.

6,8-Dimethyl-3-hydroxypyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (Fervenulone (15)). Method A. A mixture of **14** (0.227 g, 0.001 mol) and HCOOH (5 mL) was refluxed for 1 h. The reaction mixture was evaporated in vacuo, and the residue was filtered by the addition of EtOH. The mass was recrystallized from EtOH and the crystals were dried (P_2O_5) in vacuo for 2 h at 120 °C to give the

anhydrous **15** (0.186 g, 89%), mp 256–258 °C (lit.[15] mp 260–261 °C); IR 1710, 1660 cm^{-1} (CO); MS *m/e* 209 (M^+).

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 39.89; H, 3.78; N, 33.40.

Method B. A mixture of **14** (0.227 g, 0.001 mol) and 2 N HCl (3 mL) at 90 °C for 30 min. The resulting solution was neutralized with 4% NaOH and allowed to stand overnight at room temperature. The precipitates were filtered and recrystallized from EtOH. The crystals were dried under the conditions described above to yield **15** (0.107 g, 51%), mp 256–258 °C, identical with a sample prepared by method A.

Method C. A solution of 3-benzyloxy-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione **16** (1.196 g, 0.004 mol) in EtOH (100 mL) containing 10% Pd–C (1 g) was hydrogenated at room temperature and at atmospheric pressure. Hydrogenation was stopped when the theoretical volume (90 mL) of H_2 gas was consumed. The solution was filtered and the filtrate was evaporated to dryness in vacuo. The residue was treated as described in method A to give **15** (0.418 g, 50%), mp 256–258 °C, identical with the material prepared by methods A and B.

3-Benzyloxy-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (16). A suspension of **14** (2.27 g, 0.01 mol) in absolute benzyl alcohol (10 mL) dissolving metallic Na (0.24 g, 0.01 g-atom) was stirred at room temperature for 3 h. The precipitates were filtered, washed with H_2O, and recrystallized from EtOH to give **16** (2.24 g, 75%), mp 185–187 °C; IR 1735, 1675 cm^{-1} (CO); MS *m/e* 299 (M^+).

Anal. Calcd for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 55.82; H, 4.51; N, 23.07.

2,6,8-Trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (2-Methylfervenulone, MSD-92 (2)). A mixture of **15** (0.209 g, 0.001 mol), methyl iodide (0.28 g, 0.002 mol), and K_2CO_3 (0.07 g, 0.0005 mol) in dry DMF (10 mL) was stirred at 50 °C for 3 h. The solution was evaporated in vacuo and the residue was covered with EtOAc (3 mL). The insoluble solid was filtered off and the filtrate was again evaporated in vacuo. The residue was recrystallized from EtOH and the separated solid was dried at 120 °C in vacuo (P_2O_5) for 2 h to give the anhydrous **2** (0.212 g, 95%) as yellow crystals: mp 180–181 °C (lit.[15] mp 181–182 °C, lit.[18] mp 183–183.5 °C); IR 1730, 1665 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.52 (s, 3 H, NCH_3), 3.54 (s, 3 H, NCH_3), 3.93 (s, 3 H, NCH_3); UV λ_{max} (H_2O) 240 nm (log ε 4.27), 280 (3.30), 415 (3.45); λ_{max} (MeOH) 218 nm (log ε 4.10), 285 (3.86), 415 (2.95); MS *m/e* 223 (M^+).

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.12; H, 4.29; N, 31.72.

5-Acetylamino-1,3-dimethylbarbituric Acid (17). Method A. A solution of **5** (0.209 g, 0.001 mol) in a mixture of Ac_2O (2 mL) and AcOH (2 mL) was refluxed for 1 h. The reaction mixture was evaporated in vacuo and the residue was recrystallized from EtOH to give **17** (0.107 g, 50%), mp 230–231 °C; MS *m/e* 213 (M^+).

Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 44.89; H, 5.08; N, 19.76.

Method B. A solution of 5-amino-1,3-dimethylbarbituric acid 18[20] (0.171 g, 0.001 mol) and a mixture of Ac_2O (2 mL) and AcOH (2 mL) was refluxed for 1 h and the reaction mixture was treated as described above to give **17** (0.1 g, 47%), mp 230–231 °C, identical with a material prepared by method A.

5,7-Dimethylimidazo[4,5-e]-*as*-triazine-6(7*H*)-one (19). A mixture of **5** (0.209 g, 0.001 mol) and 0.5% NaOH (10 mL) was heated at 90 °C for 1 h. The resulting solution was acidified (pH 4) by the addition of AcOH and the precipitated solid was filtered. Recrystallization from EtOH gave **19** (0.066 g, 40%), mp 146–147 °C; IR 1750 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 3.31 (s, 3 H, NCH_3), 3.40 (s, 3 H, NCH_3), 10.23 (s, 1 H, C^3H); MS *m/e* 165 (M^+).

Anal. Calcd for $C_6H_7N_5O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.55; H, 4.31; N, 42.05.

Acknowledgment. The authors are grateful to Professor Fumio Yoneda of Kumamoto University for helpful discussions. The authors also thank Mr. Katsuhiko Nagahara of Kitasato University for his cooperation in spectral measurements.

Registry No.—**1**, 483-57-8; **2**, 22712-32-9; **4**, 40012-15-5; **5**, 62758-20-7; **10**, 60026-36-0; **11**, 63069-55-6; **12**, 25696-97-3; **13**, 64235-46-7; **14**, 18969-84-1; **15**, 18969-83-0; **16**, 64235-47-8; **17**, 64235-48-9; **18**, 54632-31-4; **19**, 64216-10-0; benzyl alcohol, 100-51-6.

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α-Phosphoryl Sulfoxides. 3. Dimethylphosphorylmethyl p-Tolyl Sulfoxide. Resolution, Stereospecific Synthesis, and the Horner–Wittig Reaction. A New Synthesis of Optically Active α,β-Unsaturated Sulfoxides[1]

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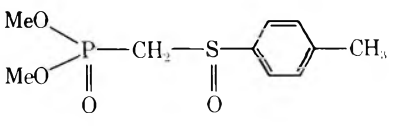
Received March 2, 1977

As part of a continuing study of α-phosphoryl sulfoxides, racemic dimethylphosphorylmethyl p-tolyl sulfoxide (1) was prepared and resolved into optical isomers via fractional crystallization of diastereomeric quininium salts of methyl-p-tolylsulfinylmethylphosphonic acid (5) and subsequent methylation of the tetramethylammonium salts of the resulting enantiomers of 5. Sulfoxide (+)-1 with the R chirality at sulfur was synthesized stereospecifically by treatment of (−)-(S)-menthyl p-tolylsulfinate (2) with dimethylphosphorylmethyllithium (4). The enantiomeric and optical purity of chiral sulfoxides 1 was determined by means of NMR spectroscopy using a chiral europium shift reagent. It was demonstrated that the lithio derivative of (+)-1 reacted with a variety of carbonyl compounds to afford optically active α,β-unsaturated sulfoxides. In some cases the formation of β,γ-unsaturated sulfoxides was observed.

α-Phosphoryl sulfoxides[2–4] are of considerable interest from both synthetic and stereochemical points of view. Like simple sulfoxides, they undergo the Pummerer and Pummerer-type reactions, halogenation, oxidation, and reduction.[5] Owing to the presence of the phosphonate moiety, α-phosphoryl sulfoxides are key substrates in the synthesis of α,β-unsaturated sulfoxides based on the Horner–Wittig reaction.[3] It should be mentioned that this reaction can be also carried out in a catalytic two-phase system in which the α-phosphoryl sulfoxides act as phase-transfer catalysts.[6–8]

Although a number of methods for preparing α,β-unsaturated sulfoxides are known,[9] synthetic approaches to their optically active analogues are few in number and for the most part of limited applicability. The majority of optically active, α,β-unsaturated sulfoxides described in the chemical literature have been prepared according to Andersen's procedure from a reaction of (−)-menthyl p-tolylsulfinate with vinyl Grignard reagents.[10] Tschuchihashi et al.[11] obtained the isomer E of optically active styryl p-tolyl sulfoxide by condensation of (+)-(R)-methyl p-tolyl sulfoxide with benzaldehyde followed by elimination of water. A method described by Naso et al.[12] consisting of an asymmetric elimination of β-halogenoethyl p-tolyl sulfoxides by optically active amines is interesting but not very useful in practice since it affords vinyl p-tolyl sulfoxide with an optical purity of less than 20%.

Therefore, with the intent of developing a general method for the synthesis of optically active α,β-unsaturated sulfoxides, we have prepared optically active α-phosphoryl sulfoxides with the optically active center at the sulfur atom. In this paper we describe the synthesis of optically active dimethylphosphorylmethyl p-tolyl sulfoxide (1) and its Horner–Wittig reaction with carbonyl compounds. This sulfoxide was chosen because of the possibility of correlating its configuration with



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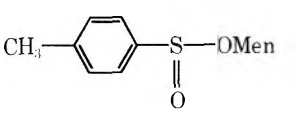

2

(−)-(S)-menthyl p-tolylsulfinate (2) which is a common precursor to many optically active sulfinyl compounds.[13,16]

Results and Discussion

Synthesis of Racemic Dimethylphosphorylmethyl p-Tolyl Sulfoxide (1) and Its Enantiomers via Optical Resolution. Racemic sulfoxide 1 was prepared in good yields by a selective oxidation of dimethylphosphorylmethyl p-tolyl sulfide (3) with sodium metaperiodate and by the reaction of the lithio derivative of dimethyl methylphosphonate (4) with methyl p-tolylsulfinate.

The presence of the phosphonate moiety in the molecule of sulfoxide 1 offers the possibility of its utilization not only in the Horner–Wittig reaction but also for the transformation of the phosphonate ester function into the corresponding phosphonic acid 5, which in turn makes possible the resolution of the chiral sulfoxide grouping by the classical method via diastereomeric salts with optically active amines. For this reason we prepared methyl p-tolylsulfinylmethylphosphonic acid (6) by two methods. In one of them sulfide 3 was used as the starting material. We found that it was readily demethylated by reaction with sodium iodide at 130–150 °C or hydrolyzed under alkaline conditions (12% aqueous NaOH–dioxane) to give the sodium salt of O-methyl p-tolylthiomethylphosphonic acid (6). The dicyclohexylammonium salt of this acid (mp 132–132.5 °C) was oxidized to the dicyclohexylammonium salt of 5 (mp 152.5–153.5 °C) from which the free acid 5 having mp 94–95 °C was liberated by passing it through an ion-exchange column.

An alternative route to 5 involved the direct alkaline hydrolysis of sulfoxide 1 which resulted in the formation of the desired product in 75% yield.

Racemic acid 5 readily formed a crystalline quinine salt, $[\alpha]_D$ −78°, which after six crystallizations from acetone afforded in 19% yield the diastereomeric salt having $[\alpha]_D$ −186°. Its specific rotation remained unchanged after further crystallizations. Decomposition of this salt gave the free acid (−)-5, $[\alpha]_D$ −142°. The more soluble diastereomeric salt having $[\alpha]_D$ −3.9° was isolated from the acetone mother liquors in 47% yield. After acidification of this salt (−)-5, $[\alpha]_D$ +103°, was obtained. Both antipodes of acid 5 were converted into their tetramethylammonium salts and treated with methyl iodide in acetonitrile to give the enantiomeric sulfoxides 1 with $[\alpha]_D$ −149° and +106°, respectively. The experiments described above are shown in Scheme I.

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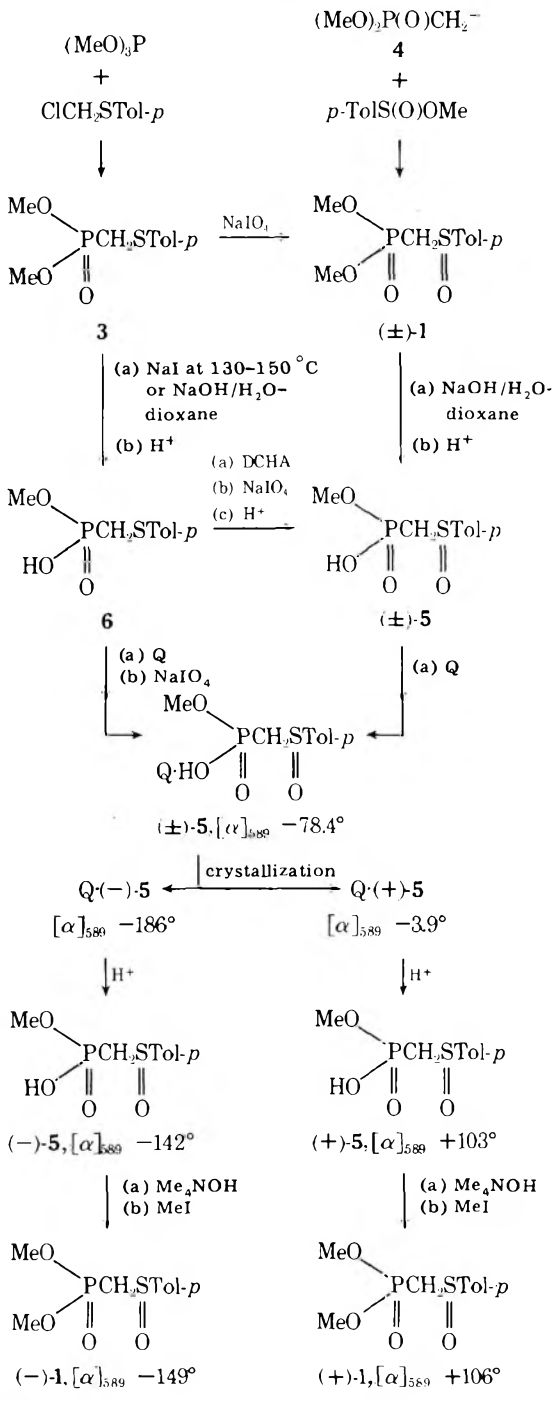
Scheme I. Synthesis of Racemic and Optically Active Dimethylphosphorylmethyl *p*-Tolyl Sulfoxide (1)



DCHA - dicyclohexylamine; Q - quinine.

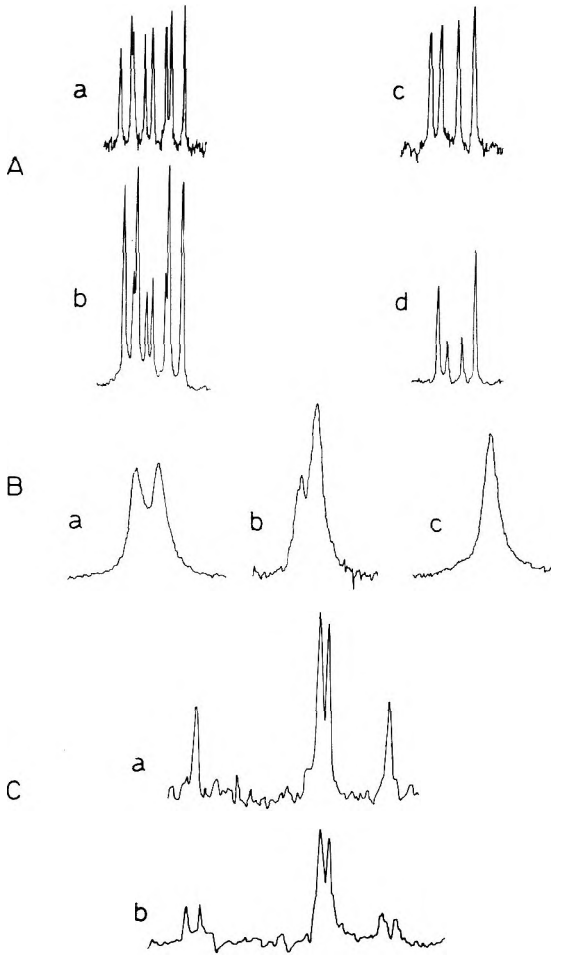


Figure 1. ^{1}H NMR (A), ^{31}P NMR (B), and ^{13}C NMR (C) spectra of sulfoxide 1 in the presence of chiral shift reagent TFMC. The ratio of 1 to TFMC was 1:2, chloroform as solvent was used. (A) Normal (a and b) and phosphorus decoupled (c and d) resonance signals of the methoxy protons: (a) (±)-1 and TFMC; (b) (+)-1, $[\alpha]_D$ +50.4°, and TFMC. (B) Proton decoupled ^{31}P NMR spectra. (a) (±)-1 and TFMC ($\Delta\delta$ = 21 Hz); (b) (−)-1, $[\alpha]_D$ −74.5°, and TFMC; (c) (−)-1, $[\alpha]_D$ −149°, and TFMC. (C) Proton decoupled ^{13}C NMR resonance signals of the methylene and methoxy carbons. (a) (±)-1 without TFMC; (b) (±)-1 in the presence of TFMC ($\Delta\delta$ = 9.8 Hz).

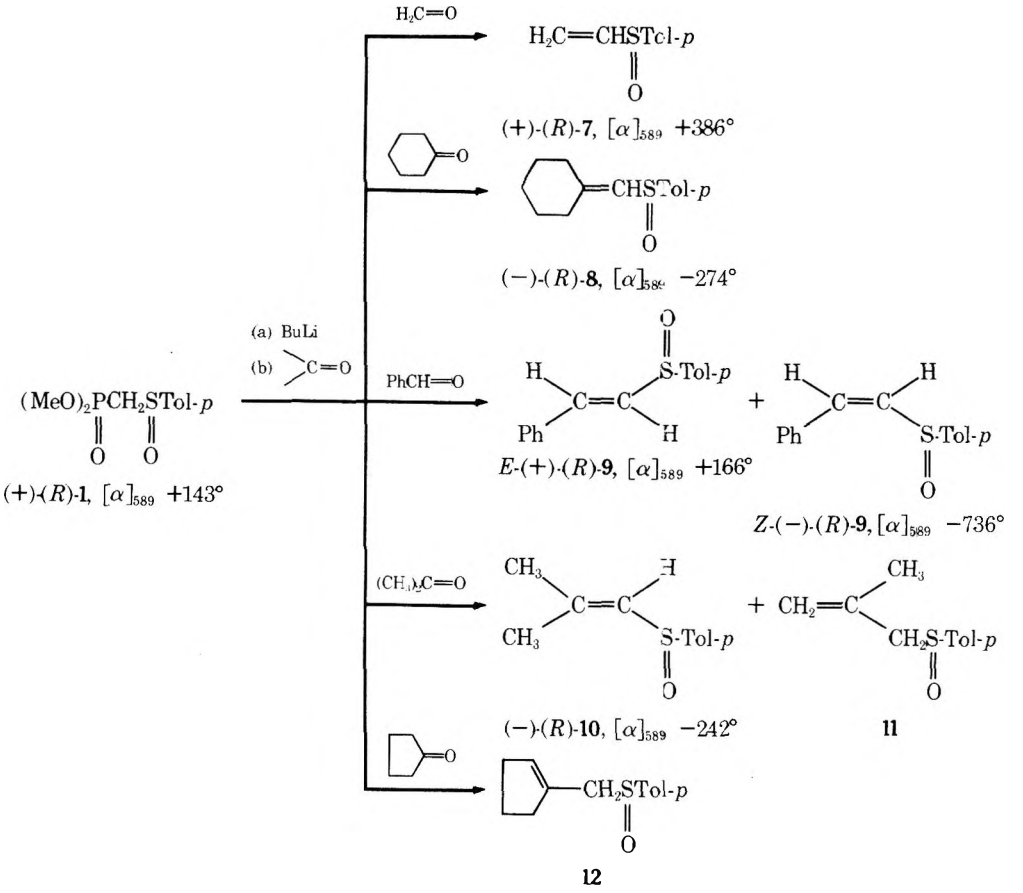
It is worthwhile to mention that our approach to optically active sulfoxides 1 is general and can be applied to any α-phosphoryl sulfoxide.

Determination of the Enantiomeric and Optical Purity of α-Phosphoryl Sulfoxide 1 by NMR. Resolution is often deemed complete once the enantiomers are obtained with equal and opposite specific rotations. This criterion, however, has limited precision and since in our case it was not fulfilled, an independent establishment of the optical purity of enantiomeric sulfoxides 1 was desirable. We employed, therefore, a chiral lanthanide shift reagent, tris-[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), (TFMC),[14] as a chiral medium for separation of the enantiomeric resonances of sulfoxide 1.

However, before these experiments are considered, it is appropriate to describe the ^{1}H NMR spectrum of sulfoxide 1. Thus, the ^{1}H NMR spectrum of 1 at 90 MHz showed, in addition to the resonance signals of the *p*-tolyl protons (singlet at δ 2.42 ppm and multiplet at δ 7.48 ppm), two doublets centered at δ 3.74 and 3.80 ppm ($J_{CH_3\text{-}P}$ = 11 Hz) which correspond to the diastereotopic methoxy groups as well as two AB systems at δ 3.29 and 3.40 ppm which are a part of the ABX system (X = phosphorus) and correspond to the nonequivalent methylene protons. It is obvious that the chiral sulfur atom in 1 induces the magnetic nonequivalence of the methoxy and methylene protons.

The ^{1}H NMR spectrum of racemic 1 in the presence of TFMC revealed further doubling of the methoxy resonance signals whereas no separation of the enantiomeric resonances was observed for the other groups of protons. Therefore, only the methoxy signals are of analytical value. As expected, the ^{1}H NMR spectrum of (+)-1, $[\alpha]_D$ +50.4°, in the presence of TFMC contained two pairs of the methoxy doublets of different intensity. The integration of these signals provided the basis for the determination of the enantiomeric (+)-1/(−)-1 ratio as 67.6:32.4 and an estimation of the specific rotation for optically pure sulfoxide 1. The calculated value was equal to $[\alpha]_D$ +143° which is in good agreement with the experimental value obtained for (−)-1 (the difference lies within the limits of error of the NMR determination). With regard to the ac-

Scheme II. The Horner–Wittig Reaction of (+)-(*R*)-Dimethylphosphorylmethyl *p*-Tolyl Sulfoxide (1) with Aldehydes and Ketones



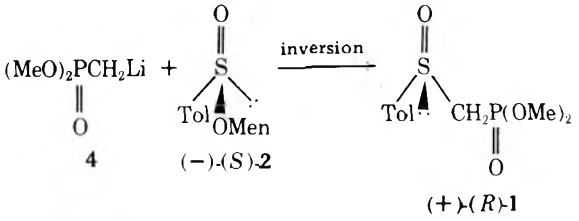
curacy of the NMR method, the phosphorus decoupled ^1H NMR spectra proved to be very useful.

The ^{31}P NMR spectra were also utilized to demonstrate that sulfoxide (−)-**1**, $[\alpha]_D$ −149°, was optically pure. In the proton decoupled ^{31}P NMR spectrum of a mixture of racemic **1** with TFMC, there were observed two well separated singlets of equal intensity due to enantiomeric sulfoxides **1**. Since in the $^{31}P\{H\}$ NMR spectrum of (−)-**1**, $[\alpha]_D$ −149° in the presence of TFMC there was only one singlet, it can be assumed that the examined sample is optically pure.

It is also of special interest to note that in the $^{13}C\{H\}$ NMR spectrum of sulfoxide **1** with TFMC, the separation of the enantiomeric resonances of the methylene carbon was observed. The ^1H, ^{31}P, and ^{13}C NMR spectra discussed above are shown in Figure 1.

Stereospecific Synthesis of (+)-(*R*)-Dimethylphosphorylmethyl *p*-Tolyl Sulfoxide (1). Although the synthesis of both enantiomers of **1** has been accomplished, the method involving optical resolution of diastereomeric quininium salts of acid **5** followed by methylation is not very satisfactory for two reasons; i.e., the total yield of enantiomeric sulfoxides **1** obtained by this procedure was not satisfactory, and the dextrorotatory isomer of **1** was obtained in only 70% optical purity. Therefore, to overcome these limitations we extended our study to the reaction of phosphonate carbanions with sulfinic esters (reported by us earlier).[4] We have now found that treatment of (−)-(*S*)-menthyl *p*-tolylsulfinate (**2**), $[\alpha]_D$ −202°, with two moles of dimethylphosphorylmethyllithium (**4**) at −20 °C in tetrahydrofuran gave the sulfoxide (+)-**1**, $[\alpha]_D$ +144° in about 70% yield.[15]

Surprisingly, this reaction resulted in the formation of the dextrorotatory sulfoxide **1** which was almost optically pure. In view of this finding, the two methods may be considered to be complementary.



The reaction described above also allowed us to assign the absolute configuration to enantiomeric sulfoxides **1**. Since this reaction is a typical nucleophilic substitution at sulfinyl sulfur and undoubtedly takes place with inversion of configuration at sulfur,[16] it is reasonabe to assume that the chirality at sulfur in sulfoxide (+)-**1** is *R*.

Synthesis of Optically Active α,β-Unsaturated Sulfoxides. Since a method for synthesizing enantiomeric sulfoxides **1** was now available, the remaining problem was to apply it for the synthesis of optically active α,β-unsaturated sulfoxides. The reaction of the lithio derivative of sulfoxide (+)-(*R*)-**1**, $[\alpha]_D$ +143°, with carbonyl compounds was carried out under conditions similar to those described previously[3] for racemic diethylphosphorylmethyl methyl sulfoxide. The results obtained from reaction of the organolithium reagent with formaldehyde, cyclohexanone, benzaldehyde, acetone, and cyclopentanone are summarized in Scheme II.

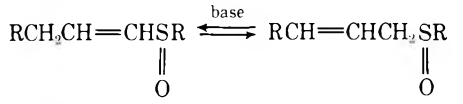
The reaction of (+)-(*R*)-**1** with formaldehyde gave (+)-vinyl *p*-tolyl sulfoxide (**7**), $[\alpha]_D$ +386° which is known to have the *R* chirality at sulfur.[10]

Taking into account the fact that the Horner–Wittig reaction of (+)-**1** does not disturb the configuration at the chiral sulfur, this result provides independent proof of correctness of our configurational assignments to the enantiomers of sulfoxide **1**. The reaction with cyclohexanone yielded sulfoxide (−)-(*R*)-**8**, $[\alpha]_D$ −274°.

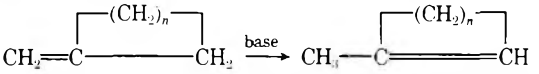
As expected, in the case of the reaction of benzaldehyde, a mixture of isomers $E + Z$ of styryl *p*-tolyl sulfoxide (*R*)-(**9**) in the ratio 75:25 was obtained. The specific rotation of the product was found to be $[\alpha]_D$ −68°. Since the isomer *E* of sulfoxide (*R*)-**9** is dextrorotatory and its specific rotation value reported in the literature[11] is $[\alpha]_D$ +164.5°, the negative sign of the specific rotation of our product must have been due to a very high rotation value of the isomer *Z*-(*R*)-**9** of opposite sign. It is noteworthy that the pure *Z* isomer of optically active sulfoxide **9** has not yet been prepared and characterized. Therefore, by means of column chromatography the initially obtained mixture of sulfoxides (*R*)-**9** was separated into the pure *E* and *Z* isomers having $[\alpha]_D$ +166° and −736°, respectively. We would like to point out that, although the chirality at sulfur in both geometrical isomers is the same, the signs of their specific rotation are opposite.

Analysis of the ^{1}H NMR spectrum of the crude product upon reaction of (+)-(*R*)-**1** with acetone revealed the presence of two olefinic compounds separable by column chromatography. The major product was the expected (−)-(*R*) 1-(*p*-tolylsulfinyl)-2-methylpropene (**10**), $[\alpha]_D$ −242° whereas the minor product has been identified as 2-methylallyl *p*-tolyl sulfoxide (**11**), i.e., the isomeric β,γ-unsaturated system. The ratio of α,β- to β,γ-unsaturated isomers **10** and **11** was found by NMR spectral analysis to be 66:34. In the case of cyclopentanone the only product obtained was β,γ-unsaturated sulfoxide **12**.[17]

Although the base-catalyzed isomerization of α,β- to β,γ-unsaturated isomers of alkenyl methyl sulfides, sulfoxides, and sulfones is well known,[18] this seems to be the first reported case of it occurring under the Horner–Wittig reaction conditions.[19] It is quite likely that the initially formed α,β-unsaturated sulfoxides undergo isomerization to the corresponding β,γ isomers under the basic reaction conditions especially in view of the fact that a small molar exesss in *n*-butyllithium was used for the generation of **4**.[20]



The isomerization rate depends on the structure of the particular sulfoxide. The exclusive formation of the β,γ-unsaturated sulfoxide **12** prepared from cyclopentanone and the stability of α,β-unsaturated sulfoxide **8** prepared from cyclohexanone are not surprising. Thus the activation parameters for the base-catalyzed isomerization of methylenecycloalkanes to methylcycloalkenes are $H^{\ddagger}$ = 13.3 kcal/mol and $S^{\ddagger}$ = −17 eu for five-membered systems, and $H^{\ddagger}$ = 27.1 kcal/mol and $S^{\ddagger}$ = 0.7 eu for six-membered systems.[21]



Finally, a comment regarding the optical activity of sulfoxides **11** and **12**; i.e., on isolation, both sulfoxides exhibited very small positive rotations. Like other optically active allyl sulfoxides, they most probably undergo fast racemization by a [2,3]sigmatropic process to give the achiral sulfenate ester as an intermediate.[22]

Experimental Section

All melting and boiling points are uncorrected. Solvents and commerical reagents were distilled and dried by conventional methods before use. ^{1}H NMR spectra were recorded at 60 MHz with a R12B Perkin-Elmer spectrometer and at 90 MHz with a Bruker HX90 spectrometer. ^{31}P and ^{13}C NMR spectra were obtained on a Jeol JNM-C-60 H1 spectrometer with external H_3PO_4 and internal Me_4Si as the standards, respectively. Column chromatography was done on Merck silica gel, 100–200 mesh. Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter in chloroform solution, unless specified otherwise.

Dimethylphosphorylmethyl *p*-Tolyl Sulfide (3). A mixture of chloromethyl *p*-tolyl sulfide (51.3 g, 0.3 mol) and trimethyl phosphite was heated at 150–160 °C for 10 h. The crude product was distilled to give **3** as a colorless oil: bp 120–122 °C (0.05 mmHg), n^{20}_D 1.5472, 51.7 g (70%); ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3, $CH_3C_6H_4$), 3.15 (d, 2, CH_2–P(O), $^1J_{P\text{-}CH_2}$ = 14 Hz), 3.74 (d, 6, CH_3OP, $^2J_{P\text{-}CH_3}$ = 10.7 Hz), 7.13 and 7.37 (A_2B_2 system, 4, aromatic, J_{AB} = 8.3 Hz); ^{31}P NMR ($CHCl_3$) δ −26.3. Anal. Calcd for $C_{10}H_{15}O_3PS$: C, 48.77; H, 6.14; P, 12.57. Found: C, 49.12; H, 6.38; P, 12.42.

Oxidation of Sulfide 3 to Dimethylphosphorylmethyl *p*-Tolyl Sulfoxide (1). To a solution of sulfide **3** (2.46 g, 0.01 mol) in 13 mL of acetone and 7 mL of water a solution of sodium metaperiodate (2.25 g, 0.0105 mol) in water was added within 1 h at −5 to 0 °C. The reaction mixture was stirred at 0 °C for 4 h and allowed to stand at 5 °C for 24 h. The precipitated sodium iodate was filtered off. After removal of acetone the water solution was extracted with chloroform (5 × 10 mL). The chloroform extract was dried over anhydrous $MgSO_4$ and evaporated to give pure sulfoxide **1** as a colorless oil: n^{23}_D 1.5295, 2.49 g (95%); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3, CH_3–C_6H_4), 3.29 and 3.40 (AB part of ABX system, 2, $CH_2P(O)$, J_{AB} = 14.55 Hz, J_{AX} = 14.65 Hz, J_{BX} = 15.43 Hz, X = phosphorus); 3.74 and 3.80 (dd, 6, CH_3OP, $^2J_{P\text{-}CH_3}$ = 11.52 and 10.94 Hz); 7.48 (A_2B_2 system, 4, aromatic); ^{13}C NMR ($CHCl_3$) δ 21.28 (s, CH_3–C_6H_4), 53.89 (d, CH_2–P, $J_{P\text{-}CH_2}$ = 137.9 Hz), 52.99 (d, CH_3OP, $^2J_{CH_3\text{-}P}$ = 6.10 Hz); 124.10, 129.95 and 142.2 (aromatic carbons); ^{31}P NMR ($CHCl_3$) δ −20.8. Anal. Calcd for $C_{10}H_{15}O_4PS$: C, 45.79; H, 5.77; P, 11.91. Found: C, 46.14; H, 5.93; P, 11.74.

Reaction of Methyl *p*-Tolylsulfinate with Lithium Dimethyl Methylphosphonate (4). To a solution of dimethyl methylphosphonate (2.48 g, 0.02 mol) in THF (30 mL) a solution of *n*-butyllithium (16 mL, 0.022 mol) in hexane was added at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 0.5 h and then a solution of methyl *p*-tolyl sulfinate (1.70 g, 0.01 mol) in THF (20 mL) was added. Stirring at −78 °C was continued for 15 min. The mixture was warmed slowly to −20 °C and quenched with aqueous ammonium chloride. After evaporation of THF and hexane, the aqueous layer was extracted with chloroform (3 × 25 mL). The chloroform solution was dried and evaporated to give a crude oil from which excess dimethyl methylphosphonate was distilled (0.01 mmHg). Dimethylphosphorylmethyl *p*-tolyl sulfoxide (**1**) obtained in this manner (2.1 g, 80%) was chromatographed [benzene–acetone (5:1)] to afford the analytically pure sulfoxide **1**. Anal. Calcd for $C_{10}H_{15}O_4PS$: C, 45.79; H, 5.77; P, 11.81. Found: C, 45.62; H, 5.64; P, 11.70. The NMR spectra were identical with those recorded for **1** described above.

Synthesis of Methyl *p*-Tolylthiomethylphosphonic Acid (6). A. Demethylation of Sulfide 3. A mixture of **3** (24.6 g, 0.1 mol) and sodium iodide (15 g, 0.1 mol) was heated for 3 h at 140–150 °C. The resulting sodium salt of acid **6** was dissolved in water (150 mL). The water solution was extracted with chloroform (2 × 25 mL) in order to remove neutral impurities. The aqueous layer was acidified and extracted with chloroform (5 × 25 mL). After drying over anhydrous $MgSO_4$ and evaporation of the chloroform solution, 14.1 g (61%) of acid **6** as a pale yellow oil, n^{21}_D 1.5615, was obtained. It was characterized as dicyclohexylammonium salt (see below).

B. Alkaline Hydrolysis of Sulfide 3. To a solution of **3** (7.38 g, 0.03 mol) in dioxane (30 mL) sodium hydroxide (3.6 g) in 10 mL of water was added. The reaction mixture was stirred at room temperature for 2 h. After neutralization and removal of dioxane, an aqueous layer was washed with chloroform (25 mL), acidified, and then extracted with chloroform (5 × 25 mL). The chloroform solution obtained after extraction of the acidic aqueous layer was dried and concentrated to give 4.18 g (60%) of acid **6**: n^{22}_D 1.5617; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3, CH_3–C_6H_4), 3.1 (d, 2, CH_2–P, $^1J_{P\text{-}CH_2}$ = 14.7 Hz), 3.67 (d, 3, CH_3OP, $^2J_{P\text{-}CH_3}$ = 12 Hz), 7.17 (A_2B_2 system, 4, aromatic); ^{31}P NMR ($CHCl_3$) δ −26.9. Anal. Calcd for $C_9H_{13}O_3PS$: C, 46.54; H, 5.64; P, 13.34. Found: C, 46.31; H, 5.73; P, 13.39.

Dicyclohexylammonium Salt of Acid 6. Compound **6** [2.78 g (0.012 mol)] was mixed with dicyclohexylamine (2.17 g, 0.012 mol). The resulting crystalline salt was washed with ether and recrystallized from acetone to yield 4.14 g (83.7%) of the desired salt: mp 132–132.5 °C; ^{31}P NMR ($CHCl_3$) δ −14.7. Anal. Calcd for $C_{21}H_{36}O_3NPS$: C, 60.99; H, 8.77; N, 3.39; P, 7.49. Found: C, 60.80; H, 8.81; N, 3.40; P, 7.57.

Quininium Salt of Acid 6. To a solution of free acid **6** (5.2 g, 0.0224 mol) in acetone an equimolar amount of quinine (8.48 g) was added. The product was recrystallized from acetone to give 12.24 g (89%) of the title salt, mp 56–57 °C $[\alpha]_D$ −99° (c, 1.7; chloroform); ^{31}P NMR ($CHCl_3$) δ−17.2 Anal. Calcd for $C_{29}H_{39}O_6N_2PS$: C, 60.84; H, 6.84; P, 5.39. Found: C, 60.91, H, 6.72; P, 5.37.

Synthesis of Methyl *p*-Tolylsulfinylmethylphosphonic Acid (5). A. Oxidation of Dicyclohexylammonium Salt of 6. To a solution of the salt (4.13 g, 0.01 mol) in water and acetone sodium metaperiodate (2.25 g, 0.0105 mol) in water was added dropwise at −5 to 0 °C. Stirring at 0 °C was continued for 3 h and the reaction mixture was allowed to stand at 0 °C overnight. After evaporation of acetone, the dicyclohexylammonium salt of acid **5** was extracted with chloroform (4 × 25 mL). The chloroform extract was dried over $MgSO_4$ and the solvent was evaporated to give the required salt which was purified by crystallization from acetone: mp 152–153.5 °C; 3.48 g (81%), ^{31}P NMR ($CHCl_3$) δ −7.9. Anal. Calcd for $C_{21}H_{36}O_4NPS$: C, 58.72; H, 8.45; N, 3.26; P, 7.21. Found: C, 59.27; H, 8.59; N, 3.28; P, 7.31.

Dicyclohexylammonium salt (2.145 g, 0.005 mol) prepared as above was passed through an ion-exchange column (Dowex 50W-X1). After evaporation of water and drying 1.23 g (100%) of a free acid **5** was obtained: mp 94–95 °C; ^1H NMR ($CDCl_3$) δ 2.4 (s, 3, CH_3–C_6H_4), 3.41 (d, 2, CH_2–P(O), $^1J_{P\text{-}CH_2}$ = 14.7 Hz), 3.7 (d, 3, CH_3OP, $^2J_{P\text{-}CH_3}$ = 11.3 Hz), 7.42 (A_2B_2 system, 4, aromatic); ^{31}P NMR ($CHCl_3$) δ −17. Anal. Calcd for $C_9H_{13}O_4PS$: C, 43.54; H, 5.28; P, 12.48. Found: C, 43.43; H, 5.27; P, 12.38.

B. Alkaline Hydrolysis of Sulfoxide 1. To a solution of sulfoxide **1** (3.93 g, 0.015 mol) in 30 mL of dioxane a solution of sodium hydroxide (1.8 g, 0.045 mol) in 15 mL of water was added dropwise. The reaction mixture was stirred for 2 h at room temperature and treated then with 50 mL of water. After evaporation of dioxane, the aqueous layer was washed with chloroform, acidified with hydrochloric acid, and washed once with chloroform. On evaporation of water the residue was extracted with chloroform (5 × 25 mL). The solvent was evaporated to give 2.82 g (75.7%) of acid **5**, physical and spectral properties of which were identical with those described above.

Oxidation of Quininium Salt of Acid 6. To a solution of quininium salt of **6** (12.21 g, 0.02 mol) in acetone and water a solution of sodium metaperiodate (4.49 g, 0.021 mol) in water (75 mL) was dropped below 0 °C. The reaction mixture was stirred for 4 h at 0 °C and the resulting quininium salt of acid **5** was isolated by extraction with chloroform (5 × 25 mL) and the usual work-up: 11.6 g (93%), mp 50–57 °C; $[\alpha]_D$ −75° (*c* 1.7 $CHCl_3$); ^{31}P NMR ($CHCl_3$) δ −10.4. Anal. Calcd for $C_{29}H_{41}O_8N_2PS$: C, 55.58; H, 6.92; P, 4.94. Found: C, 55.94; H, 6.29; P, 5.01.

Quininium Salt of Acid 5. Alternatively, the title salt was prepared by mixing acid **5** (0.248 g, 0.001 mol) and quinine (0.3785 g, 0.001 mol) in acetone (15 mL). Evaporation of the solvent yielded 0.6265 g of the desired salt: mp 52–59 °C $[\alpha]_D$ −78.4° (*c* 1.55, $CHCl_3$).

The Resolution of Methyl *p*-Tolylsulfinylmethylphosphonic Acid (5) via Quininium Salt. The title salt (6.26 g) was crystallized from acetone (750 mL). On cooling, 1.75 g of salt, $[\alpha]_D$ −147° (*c* 1.8, $CHCl_3$) was collected, then recrystallized five times from acetone to give 1.18 g (19%) of a diastereomeric head crop, mp 181–182 °C $[\alpha]_D$ −186° (*c* 1.9, $CHCl_3$), ^{31}P NMR ($CHCl_3$) δ −10.4. This salt on passing through the ion-exchange column gave 0.465 g of acid (−)-**5**, $[\alpha]_D$ −142° (*c* 1.2, $CHCl_3$).

The mother liquor was concentrated and the residue was recrystallized from acetone to afford a salt $[\alpha]_D$ −43° (*c* 1.7, $CHCl_3$). Subsequent recrystallizations of this salt from acetone–ether (2:1) yielded 2.96 g (47%) of the salt $[\alpha]_D$ −3.9° (*c* 1.65, $CHCl_3$), the rotation of which remained unchanged after further crystallizations. The acid (+)-**5** (0.947 g) recovered from this salt has $[\alpha]_D$ +103° (*c* 1.31, $CHCl_3$)

Optically Active Sulfoxide (−)-1. Acid (−)-**5**, $[\alpha]_D$ −142° (0.232 g, 0.000935 mol) was dissolved in water (50 mL) and neutralized with a 25% aqueous solution of tetramethylammonium hydroxide. On evaporation, the tetramethylammonium salt of acid (−)-**5** was obtained, ^{31}P NMR ($CHCl_3$) δ −8.5.

The above prepared salt (0.323 g) was refluxed for 2 h with an excess of methyl iodide in acetonitrile (50 mL). After removal of the solvent, the residue was dissolved in water (40 mL) and extracted with chloroform (5 × 10 mL). The chloroform solution was evaporated to give the crude sulfoxide (−)-**1** which was purified by column chromatography using benzene–acetone (5:1) as the eluent. (−)-**1**, $[\alpha]_D$ −149° (*c* 1.16, acetone), 0.156 g (62.5%). Anal. Calcd for $C_{10}H_{15}O_4PS$: C, 45.79; H, 5.77; P, 11.91. Found: C, 46.07; H, 5.84; P, 11.59.

Optically Active Sulfoxide (+)-1. Similarly, (+)-**1**, $[\alpha]_D$ +106° (c 1.7, acetone) was prepared from (+)-**5**, $[\alpha]_D$ +103° (*c* 1.31, $CHCl_3$) in 61.5% yield.

Preparation of Sulfoxide (+)-(R)-1 from (−)-(S)-Menthyl *p*-tolylsulfinate (2). To a solution of the lithium derivative of dimethyl methylphosphonate (0.02 mol) prepared as described above a solution of (−)-(S)-menthyl *p*-tolylsulfinate (2.94 g, 0.01 mol), $[\alpha]_D$ −202° (c 1.2, acetone) in 20 mL of THF was added at −78 °C. After 15 min the reaction mixture was warmed to −20 °C and quenched with aqueous ammonium chloride. After evaporation of the organic solvents (THF, hexane) the aqueous layer was extracted with petroleum ether (to remove menthol) and then with chloroform (3 × 25 mL). The chloroform solution was dried and evaporated. Careful removal of dimethyl methylphosphonate under reduced pressure gave 1.87 g (72%) of (+)-(*R*)-**1**. The analytically pure sample of this sulfoxide, $[\alpha]_D$ +144° (c 1.0, acetone), was obtained after column chromatography using benzene–acetone (5:1) as the eluent. Anal. Calcd for $C_{10}H_{15}O_4PS$: C, 45.79; H, 5.77; P, 11.81. Found: C, 45.53; H, 5.71; P, 11.72.

Synthesis of Optically Active α,β-Unsaturated Sulfoxides and β,γ-Unsaturated Sulfoxides from (+)-(*R*)-1 and Carbonyl Compounds. All the sulfoxides listed in Scheme III were obtained according to the general procedure for the Horner–Wittig reaction of diethylphosphorylmethyl methyl sulfoxide with carbonyl compounds described previously.[3] The isolation procedure as well as the physical and spectral data of sulfoxides **7**–**12** follow.

(+)-(*R*)-*p*-Tolylsulfinylethylene (7). Column chromatography [benzene–acetone (200:3)] of the crude product from paraformaldehyde (0.15 g, 0.005 mol) and sulfoxide (+)-(*R*)-**1** (1.31 g, 0.005 mol), $[\alpha]_D$ +143°, gave 0.62 g (75%) of sulfoxide (+)-(*R*)-**7**, $[\alpha]_D$ +386° (*c* 0.98, ethanol), n^{25}_D 1.5747; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3, CH_3–C_6H_4), 5.70–6.78 (m, 3, —CH=CH_2, ABC system), 7.35 (m, 4, aromatic). Anal. Calcd for $C_9H_{10}OS$: C, 65.10; H, 6.00. Found: C, 65.01; H, 6.11.

(−)-(*R*)-1-[(*p*-Tolylsulfinyl)methylene]cyclohexane (8). The reaction of cyclohexanone (0.49 g, 0.005 mol) and (+)-**1** was carried out according to the standard procedure and the crude product was chromatographed [benzene–acetone (200:3)] to give 0.935 g (80%) of (−)-(*R*)-**8**, $[\alpha]_D$ −272° (*c* 0.85, acetone); ^1H NMR δ 1.62 [m, 6, $(CH_2)_2CH_2$-], 2.22 [m, 4, $(CH_2)_2C$=], 2.38 (s, 3, CH_3–C_6H_4), 5.94 (s, 1, CH=C-), 7.37 (m, 4, aromatic). Anal. Calcd for $C_{14}H_{18}OS$: C, 71.75; H, 7.74. Found: C, 71.98; H, 7.85; n^{22}_D 1.5610.

Styryl *p*-Tolyl Sulfoxide (9). The crude product (1.15 g, 95%), $[\alpha]_D$ −68° (*c* 1.08, chloroform), obtained from benzaldehyde (0.56 g, 0.005 mol) was a mixture of *E* and *Z* isomers in a ratio of 69:31. Column chromatography [benzene–acetone (200:3)] afforded both pure geometrical isomers of the title sulfoxide.

(*E*)-(+)-(*R*)-**9**: $[\alpha]_D$ +166° (c 1.14, chloroform); mp 82 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3, CH_3–C_6H_4), 6.72 (part of AB system, 1, J_{AB} = 15.3 Hz), 7.16–7.56 (m, 10, aromatic and a part of AB system). Anal. Calcd for $C_{15}H_{14}OS$: C, 74.35; H, 5.82. Found: C, 74.37; H, 6.02.

(*Z*)-(−)-(*R*)-**9**: $[\alpha]_D$ −736° (c 1.04, chloroform), mp 52–52.5 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3, CH_3–C_6H_4), 6.38 and 7.04 (AB system, 2, vinyl protons, J_{AB} = 10.7 Hz), 7.16–7.58 (m, 9, aromatic). Anal. Calcd for $C_{15}H_{14}OS$: C, 74.35; H, 5.82; Found: C, 74.30; H, 5.88.

(−)-(*R*)-1(*p*-Tolylsulfinyl)-2-methylpropylene (10) and 2-Methylallyl *p*-Tolyl Sulfoxide (11). From acetone (0.29 g, 0.005 mol) and an equimolar amount of (+)-**1** the crude product was obtained as a pale yellow oil: 0.895 g (92%), $[\alpha]_D$ −80° (*c* 1.06, chloroform). It consisted of 76 and 24% of **10** and **11**, respectively. Column chromatography [benzene–acetone (200:3)] afforded pure α,β-unsaturated sulfoxide **10** and β,γ-sulfoxide **11** containing ca. 10% of impurities.

(−)-(*R*)-**10**: $[\alpha]_D$ −242° (c 1.29, chloroform), mp 65°C, 0.49 g (50.5%); ^1H NMR ($CDCl_3$) δ 1.88 and 2.16 (two s, 6H, $(CH_3)_2C$=), 2.38 (s, 3, CH_3–C_6H_4), 6.10 (s, 1, -CH-C=), 7.46 (m, 4, aromatic). Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26. Found: C, 68.11; H, 7.22.

11: 0.17 g (17.5%), ^1H NMR ($CDCl_3$) δ 1.80 (s, 3, CH_3-C=), 2.38 (s, 3, CH_3–C_6H_4), 3.30 and 3.53 (AB system, 2, -CH_2-S(O), J_{AB} = 10 Hz), 4.80 and 5.00 (two s, 2, CH_2=C), 7.50 (m, 4, aromatic).

1-*p*-Tolylsulfinylmethyl Cyclopentene (12). Cyclopentanone (0.42 g, 0.005 mol) and (+)-**1** gave, after the usual work-up, crude **12** (1.10 g, 100%) as a pale yellow oil. Column chromatography afforded 0.76 g (69%) of pure **12**: mp 48.5 °C; ^1H NMR ($CDCl_3$) δ 1.80–2.30 (m, 6, ring methylene protons), 2.35 (s, 3, CH_3–C_6H_4), 3.53 [broad s, 2, $CH_2S(O)$], 5.68 (broad s, 1, ring methine proton), 7.48 (m, 4, aromatic). Anal. Calcd for $C_{13}H_{16}OS$: C, 70.86; H, 7.32. Found: C, 70.63; H, 7.32.

Registry No.—(±)-**1**, 63231-19-6; (−)-**1**, 63268-43-9; (+)-(*R*)-**1**, 61187-71-1; (−)-(*S*)-**2**, 1517-82-4; **3**, 63231-20-9; **4**, 756-79-6; (±)-**5**, 63231-21-0; (±)-**5** DCHA, 63231-22-1; (−)-**5**, 63231-23-2; (−)-**5** Q, 63231-24-3; (−)-**5** Me_4N, 63231-26-5; (+)-**5**, 63231-27-6; (+)-**5** Q, 63301-42-8; **6**, 63231-28-7; **6** Na, 63231-29-8; **6** DCHA, 63231-30-1; **6** Q, 63231-31-2; (+)-(*R*)-**7**, 54828-68-1; (−)-*R*-**8**, 63231-32-3; (*E*)-(+)-(*R*)-**9**, 41103-85-9; (*Z*)-(−)-(*R*)-**9**, 63268-44-0; (−)-(*R*)-**10**, 63269-85-2; **11**, 37616-05-0; **12**, 63231-33-4; chloromethyl *p*-tolylsulfide, 34125-84-3; trimethyl phosphite, 121-45-9; methyl *p*-tolylsulfinate, 672-78-6; quinine, 130-95-0.

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Heavy-Atom Effect on the Photodimerization of Acenaphthylene: Substituent Analysis on the Efficiency of External Aromatic Perturbers

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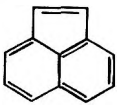
Received May 20, 1977

The photodimerization of acenaphthylene in the presence of various para-substituted bromobenzenes in methanol was studied in order to determine if the photochemical heavy-atom effect responds to a substituent change. A substituent effect was indeed observed, but the photodimer ratios do not vary linearly with Hammett's σ constants.

The photodimerization of acenaphthylene (**1**) in the presence of organic halides provides an excellent illustration of the photochemical heavy-atom effect. This reaction has been studied thoroughly by Cowan, Drisko, and Koziar, who employed standardized irradiation conditions so that syn/anti dimer ratios associated with various solvent systems could be compared.[1-7] For example, when **1** was irradiated in cyclohexane, the syn/anti photodimer ratio was determined to be 4.17, but, when *n*-propyl bromide was the solvent, the ratio dropped to 0.41.[1] These results can be explained if it is assumed that the syn dimer is derived primarily from an excited singlet state (or excimer) of **1** and that the anti dimer is de-



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rived from an excited triplet state. The heavy-atom solvent, *n*-propyl bromide, promotes singlet → triplet intersystem crossing, a perturbation that eventuates in a higher relative yield of anti dimer and a lower syn/anti ratio. The dimer ratio is also sensitive to the nature of the heavy atom, RI being a more effective "perturber" than RBr, while RCl is relatively ineffective.[3] In binary solvents of the type cyclohexane/RX, the syn/anti ratio varies inversely with the mol % of RX.[2,4]

An analysis of the influence of substituents on the efficiency of external aromatic heavy-atom perturbers has not yet been reported for a photochemical process. However, an interesting structure–efficiency relationship has been noted for a photophysical process. McGlynn and his co-workers observed that the T←S absorption band in the electronic spectrum of 1-chloronaphthalene was enhanced when that compound was codissolved with various alkyl iodides, the degree of enhancement conforming to the following trend: CH_3I > CH_3CH_2I > $CH_3CH_2CH_2I$ > $(CH_3)_2CHCH_2CH_2I$.[7] Thus, the heavy-atom perturbation *decreased* as the electron-donating capacity of the alkyl group *increased*. Consistent with this trend is the observation that *p*-fluorobromobenzene caused more T←S enhancement in 1-chloronaphthalene than did bromobenzene.[7]

Results and Discussion

In this paper, we report an investigation of the photodimerization of acenaphthylene in the presence of various para-substituted bromobenzenes dissolved in methanol. Dimer ratios were determined at aryl bromide concentration levels of 0.1, 0.4, 0.7, 1, 2, 4, 6, 8, and 10 mol %, and the substituents that were studied include H, CH_3, OCH_3, CHO, and CF_3. The substituents NH_2, COOH, and CN were not studied because the corresponding aryl bromides are not sufficiently soluble in methanol over the concentration range of interest to us. Methanol was chosen as the cosolvent instead of cyclohexane because a broader range of syn/anti ratios is accessible with methanol.[1] We report two complete sets of data; i.e., for each aryl bromide at each concentration level, two reactions were conducted, but they were not run at the same time. One set of data was first collected for *all* aryl bromides, and then another data set was collected. The results are presented in Table I.

0022-3263/78/1943-0478$01.00/0

Table I.[a] UV Irradiation of 1 in p-XC_6H_4Br/Methanol

p-XC_6H_4Br mol %	Syn/anti ratio									
	H		CH_3		OCH_3		CHO		CF_3	
	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2
0.1	4.85	4.97	4.60	4.48	3.68	3.66	3.00	2.97	3.52	3.36
Av	4.91		4.54		3.67		2.99		3.44	
0.4	3.53	3.63	3.17	3.17	2.76	2.72	1.72	1.68	1.75	1.88
Av	3.58		3.17		2.74		1.70		1.82	
0.7	2.39	2.35	2.21	2.16	2.07	1.94	1.23	1.14	1.08	1.16
Av	2.37		2.19		2.01		1.19		1.12	
1.0	2.30	2.28	2.04	2.06	1.60	1.67	1.04	0.83	1.00	0.96
Av	2.29		2.05		1.64		0.94		0.98	
2.0	1.91	1.83	1.55	1.62	1.32	1.34	0.83	0.78	1.03	0.99
Av	1.87		1.59		1.33		0.81		1.02	
4.0	1.23	1.30	1.19	1.16	1.24	1.03	0.51	0.51	0.82	0.84
Av	1.27		1.18		1.14		0.51		0.83	
6.0	1.08	1.14	1.20	1.17	0.70	0.65	0.45	0.44	0.74	0.65
Av	1.11		1.19		0.68		0.44		0.70	
8.0	0.95	1.06	0.92	1.02	0.58	0.58	0.35	0.32	0.33	0.24
Av	1.01		0.97		0.58		0.34		0.29	
10.0	0.79	1.01	0.57	0.68	0.55	0.53	0.16	0.11	0.21	0.23
Av	0.90		0.63		0.54		0.14		0.22	

[a] Eight blank samples were also photolyzed, four of which contained 1.0 g of 1 in methanol (total volume 10 mL) and four of which contained 1.5 g of 1 in methanol (total volume 15 mL). See the Experimental Section for more details. The observed syn/anti ratios were 6.29, 6.59, 6.32, 6.70, 6.27, 6.43, 6.56, and 6.23 (av 6.42). These values may be compared to a literature value of 5.74.[1]

Table II[a]

Authentic dimer mixtures			UV analysis of mixtures	
Wt of syn dimer, mg	Wt of anti dimer, mg	Syn/anti ratio	Syn/anti ratio	Error, %
11.42	1.71	6.68	6.50	2.7
11.13	1.63	6.83	6.68	2.2
10.90	2.14	5.09	5.15	1.1
10.84	2.11	5.14	5.03	2.1
9.71	3.29	2.95	2.86	3.1
9.66	3.27	2.95	2.87	2.7
8.76	4.41	1.99	2.06	3.5
8.62	4.18	2.06	1.99	3.4
6.61	6.73	0.98	1.02	4.1
6.48	6.23	1.04	1.01	2.9
5.38	7.91	0.68	0.71	4.2
4.34	8.34	0.52	0.55	5.8
3.25	9.85	0.33	0.36	9.1
3.19	10.29	0.31	0.34	9.7

[a] It can be seen that the average error in the determination of syn/anti ratios by the UV method is about 4% and is somewhat lower for high ratios than it is for low ratios. The error is sufficiently low, however, so that *relative* ratios are pretty much maintained as one proceeds from one perturber to the next at the various concentration levels.

Irradiations of 1 were conducted with a 450-W, Ace-Hanovia 6515-34 quartz mercury-vapor lamp fitted with a uranium glass sleeve and a merry-go-round apparatus such that the sample tubes were placed 7.5 cm from the light source. Each reaction solution, containing acenaphthylene and solvent (10%, w/v), was degassed, and each Pyrex reaction vessel was sealed prior to irradiation. The irradiations were continued for 15 h at room temperature, during which time the photodimers precipitated from solution. The crude dimer mixtures were subsequently isolated, washed with methanol to remove any unreacted 1, and subjected to UV analysis. A determination of absorbances for each mixture at *two* wavelengths coupled with a knowledge of extinction coefficients for the pure dimers at those wavelengths allowed the computation of syn/anti ratios. An assessment of the accuracy of this analytical method, first utilized by Cowan and Drisko,[4] is presented in Table II. Authentic dimer mixtures were prepared from the pure dimers, and the known ratios were compared to those determined by UV analysis.

The syn and anti photodimers of 1 exhibit measurable solubilities in p-X-C_6H_4-Br/CH_3OH. Thus, the ratios presented in Table I require correction because they were determined by analysis of dimers which had precipitated and do not account for the quantity of dimers which remained in solution. If the dimers exhibited *identical* solubilities corrections would be unnecessary, but they do not. Fortunately, in those instances where solubilities were determined, the corrections did not lead to serious changes, and most of the discussion herein pertains to uncorrected ratios. Dimer solubilities in XC_6H_4Br/CH_3OH at the 0.1 and 10 mol % extremes of aryl bromide concentration were measured. Corrected and uncorrected syn/anti ratios are compared in Table III.

Inspection of Table I indicates clearly that *most* of the heavy-atom perturbation is achieved by the time concentration levels of ArBr in methanol have reached 1–2 mol %. Although the various aryl bromides do not appear to differ greatly in their ability to reduce syn/anti ratios (i.e., to promote S ⇝ T), they do differ, and the difference seems to be real. There also seems to be a clear indication that electrophilic substituents enhance the heavy-atom effect. For example, at the 1 mol % ArBr level, syn/anti ratios of 2.05 (CH_3), 1.64 (OCH_3), 0.94 (CHO), and 0.98 (CF_3) were observed. However, those ratios do not correlate with Hammett's σ constants. For example, p-CH_3 (σ −0.170) is more electrophilic than p-OCH_3 (σ −0.268). Yet, the latter substituent induces a lower syn/anti ratio. Similarly, p-CF_3 (σ +0.54) is more electrophilic than p-CHO (σ +0.51) but less effective in lowering the syn/anti ratio. Finally all the substituted bromobenzenes studied by us were better perturbers than bromobenzene itself *when methanol was the solvent*, a curious fact for which we have no explanation.

It has been demonstrated by Hartmann, Hartmann, and Schenck that acenaphthylene photodimer ratios depend on the dielectric constant of the reaction medium.[10] A plot of log ([anti]/[syn]) vs. $(D - 1/2D + 1)(\rho/M)(10^2)$ for *eleven* solvents gave a straight line with a negative slope.[10] It seems possible, then, that the trends reported herein may manifest differences in dielectric for the binary "solvents" p-X-C_6H_4-Br/CH_3OH and have little or nothing to do with substituent perturbations

Table III. Solubility Corrections for Syn/Anti Dimer Ratios

p-XC_6H_4Br, X	Registry no.	0.1 mol % ArBr		10 mol % ArBr	
		Uncorrected	Corrected	Uncorrected	Corrected
H	108-86-1	4.96	4.96	1.10	1.06
CH_3	106-38-7	4.46	4.53	0.86	0.91
OCH_3	104-92-7	3.69	3.71	0.53	0.58
CHO	1122-91-4	2.98	3.00	0.11	0.14
CF_3	402-43-7	3.38	3.40		

Table IV[a]

p-XC_6H_4Br	p-XC_6H_4Br in CH_3OH, mol %								
	0.1	0.4	0.7	1	2	4	6	8	10
X = CH_3									
Yield, g	0.30	0.33	0.35	0.38	0.80	0.96	1.17	1.24	1.25
	0.34	0.34	0.33	0.28	0.95	0.91		1.20	1.21
Av yield, %	32	34	37	33	58	62	78	81	82
X = OCH_3									
Yield, g	0.21	0.31	0.33	0.38	0.88	1.00	1.13	1.09	1.08
	0.30	0.37	0.33	0.40	0.85	0.94	0.98	1.08	1.07
Av yield, %	25	34	33	39	58	65	70	72	72
X = H									
Yield, g	0.28	0.31	0.37	0.43	0.67	0.91	1.12	1.09	1.26
	0.36	0.36	0.33	0.41	0.77	0.94	1.06	1.15	1.25
Av yield, %	32	34	33	42	48	62	73	75	84
X = CF_3									
Yield, g	0.34	0.41	0.41	0.42	0.80	1.17	1.21	1.29	1.27
	0.28	0.38	0.40	0.46	0.77		1.11	1.26	1.26
Av yield, %	31	40	41	44	52	78	77	85	84
X = CHO									
Yield, g	0.33	0.35	0.35	0.39	0.79	0.89	1.25	1.16	1.30
	0.35	0.38	0.41	0.44	0.63	1.19		1.34	1.22
Av yield, %	34	37	38	42	47	69	83	83	84

[a] Eight blank samples were also photolyzed, four of which contained 1.0 g of I in methanol (total volume 10 mL) and four of which contained 1.5 g of I in methanol (total volume 15 mL). See Table I and the Experimental Section. The observed yields were 0.20 (20%), 0.18 (18%), 0.19 (19%), 0.21 (20%), 0.23 (15%), 0.35 (23%), 0.32 (21%), and 0.18 g (12%). These may be compared to a literature value of 42.5% reported by Cowan and Drisko for their standardized conditions.[1]

on the heavy atom. However, while it seems likely that solvent dielectric constants will differ significantly at ArBr concentration levels near 10 mol %, they will differ very little at ArBr concentration levels near 1 mol %. For example, the dielectric constants of methanol and bromobenzene are 32.63 and 5.40, respectively, at 25 °C.[11] On the assumption that the dielectric constant for a binary liquid can be approximated by (mol fraction of A)(dielectric constant of A) + (mol fraction of B)(dielectric constant of B), dielectric constants of 29.91, 32.35, and 32.60 can be computed for bromobenzene in methanol at the 10, 1, and 0.1 mol % concentration levels. For p-bromoanisole (D = 7.06 at 30 °C),[12] the corresponding computed D values are 30.07, 32.37, and 32.60. The fact that the relative syn/anti ratios in this study follow the same substituent trend at 10 mol % ArBr in methanol as at 0.1 mol % ArBr in methanol (where dielectric constants are nearly identical) indicates that solvent dielectric is not a serious controlling factor here.

We have, at this time, no information concerning possible light absorption by the heavy-atom solvents and subsequent energy transfer from them to acenaphthylene, nor have we assessed the possibility of direct reactions between acenaphthylene and the aryl bromides.

Experimental Section

General. Acenaphthylene and all of the substituted bromobenzenes used in this investigation were purchased from the Aldrich Chemical Co. and were designated as 99% pure. Acenaphthylene was recrystallized twice from 95% ethanol (mp 90–91 °C), and p-bromobenzaldehyde was recrystallized twice from 95% ethanol (mp 57–58 °C). Bromobenzene (bp 154–156 °C), p-bromotoluene (bp 183–185 °C), p-bromoanisole (bp 215–216 °C), and p-bromobenzotrifluoride (bp 154–155 °C) were distilled prior to use.

Ultraviolet spectra were recorded on a Cary-17 UV–vis–near-IR spectrophotometer. All melting points and boiling points recorded herein are uncorrected.

Reaction Mixtures. Acenaphthylene (2.50 g) was dissolved in each binary solvent and diluted volumetrically with that solvent to 25 mL. A 10-mL aliquot (for solvents 0.1–1 mol % in ArBr) or a 15-mL aliquot (for solvents 2–10 mol % in ArBr) was subsequently removed and transferred to a Pyrex tube (25 cm long × 12 mm wide × 1 mm thick). Each reaction mixture was then degassed by two freeze (liquid N_2)–pump–thaw cycles, and each reaction vessel was sealed under vacuum.

Irradiation Procedure. Irradiations were conducted with a 450-W, Ace-Hanovia 6515-34 quartz mercury-vapor lamp fitted with a uranium glass sleeve and immersed in a Vycor cooling well. The reaction vessels were placed in a merry-go-round apparatus and situated 7.5 cm from the light source. For each set of data, 45 reaction mixtures were irradiated, but they could not be irradiated all at once. They were divided into batches of 20 (0.1–1.0 mol % in ArBr; all substituents), 15 (2–10 mol % in ArBr; H, CH_3, and OCH_3 substituents), and 10 (2–10 mol % in ArBr; CHO and CF_3 substituents). The first batch was accompanied with two "blanks" (I in pure methanol), and the remaining batches were accompanied with one blank sample each. Thus, for both sets of data, eight blank samples were irradiated. The irradiations were continued for 15 h at room temperature, during which time the acenaphthylene photodimers precipitated from solution. The temperature of the reaction mixtures was ~30 °C during photolysis.

Product Analysis. The photodimers were isolated by filtration and washed with methanol (10 mL) to remove any I that may have coprecipitated during the reaction. The weights of dimer and percent conversions to dimer are summarized in Table IV for two sets of reactions. The dimer mixtures were then thoroughly powdered and subjected to UV analysis.

Solubility Measurements. The syn or anti photodimer (0.50 g) was added to 25 mL of a given solvent, and the mixture was allowed to stand with shaking for 20 h at ~22–24 °C. The insoluble material was subsequently removed by filtration, and the filtrate was con-

Table V

	Syn/anti ratio	Yield, g
Not degassed	2.65	0.513
	2.62	0.481
Degassed (2 cycles)	2.43	0.533
	2.46	0.524
Degassed (5 cycles)	2.44	0.534
	2.38	0.535

centrated to the residual solid which had dissolved. The *residue* was then weighed.

Isolation of the Anti Dimer. Acenaphthylene (10 g) was dissolved in 50 mL of *p*-OHC–C_6H_4–Br (20 mol %)/benzene and irradiated (*without* prior degassing) for 25 h. The crude product which had precipitated was isolated, washed with three portions (500 mL total) of hot cyclohexane, and recrystallized from benzene as white needles: mp 301–302 °C (lit. mp 306–307 °C);[9] UV (cyclohexane) 219 (ϵ 6.56 × 10^4), 225 nm (ϵ 1.11 × 10^5).

Isolation of the Syn Dimer. A solution of acenaphthylene (10 g) in methanol (50 mL) was degassed and irradiated for 25 h. The crude product which precipitated was isolated, and a portion of it was recrystallized from cyclohexane as white prisms: mp 232–234 °C (lit. mp 232–234 °C);[9] UV (cyclohexane) 219 (ϵ 1.10 × 10^5), 225 nm (ϵ 4.99 × 10^4).

Control. Photostability of Acenaphthylene Photodimers. The pure anti dimer (1.0 g, see above) was added to a sufficient quantity of methanol so that the final volume was 10 mL, and the resulting solid/liquid mixture was degassed and irradiated for 15 h in the usual fashion. Ultraviolet analysis of the insoluble "product" gave a syn/anti dimer ratio of 0.18.

The pure syn dimer was treated analogously and gave a syn/anti ratio of 4.37.

Control. Syn/Anti Ratios as a Function of Sample Degassing. In all of the reactions previously described, the reaction mixtures were degassed by *two* freeze–pump cycles. That two cycles are sufficient is indicated by the following study. Six reaction mixtures were prepared, each containing 1.0 g of acenaphthylene in 1.0 mol % of bromobenzene in methanol (total volume 10 mL). Two reaction mixtures were *not* degassed, two were degassed with *two* freeze (liquid N_2)–pump–thaw cycles, and two were degassed with *five* freeze–pump–thaw cycles. After irradiation and product analysis in standard fashion, the syn/anti ratios and dimer yields were obtained (Table V).

Registry No.—1, 208-96-8; *syn*-1 photodimer, 15065-28-8; *anti*-1 photodimer, 14620-98-5.

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Nucleosides. 108. Ribo–Xylo Interconversions of 6,5′-Cyclopyrimidine Nucleosides via Autoxidation and Retro-Aldol Reactions[1,2]

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Received July 14, 1977

The 5′*S* and 5′*R* epimers of 6,5′-cyclouridine undergo autoxidation to 5′-oxo-6,5′-cyclouridine when treated with oxygen and 1 N NaOH. 5′-Oxo-6,5′-cyclouridine is stable in 1 N NaOH, but under less strongly alkaline conditions, e.g., ethanolic ammonia, it undergoes 3′ epimerization to give 6,5′-cyclo-5′-oxo-1-(β-D-xylofuranosyl)uracil, probably via formation and recyclization of a pyrimido[1,6-*c*][1,3]oxazine intermediate generated by retro-aldol cleavage. The 5′-carbonyl group of 5′-oxo-6,5′-cyclouridine is predominately hydrated in aqueous systems, whereas the 5′-oxo-xylo isomer exists as the keto form under the same conditions. These ribo–xylo epimers consequently show large differences in ultraviolet spectral properties in water that are useful in monitoring the retro-aldol equilibrium reaction. Similar differences in the UV spectra of hydrated orotaldehyde (261 nm) and anhydrous orotaldehyde (300 nm) were noted. Reduction of 5′-oxo-6,5′-cyclouridine with sodium cyanoborohydride in acetic acid affords only 6,5′(*S*)-cyclouridine. Similar reduction of the 5′-oxo-xylo nucleoside affords both 5′*S* and 5′*R* epimers of 6,5′-cyclo-1-(β-D-xylofuranosyl)uracil in a ratio of 5:1, possibly indicating that the 5′*R*-xylo isomer is formed via participation of the 3′-hydroxyl group. The identity of each xylo 5′ epimer was established from NMR spectra and by the ready formation of a 3′,5′-*O*-isopropylidene derivative of the 5′*S* epimer.

Nucleosides and nucleotides restricted to one type of conformation, but retaining a full complement of hydrogen-bonding sites, are useful for probing the conformational factors that affect the specificities of the enzymes of nucleic acid metabolism.[3] In this regard, we have previously reported[4] the synthesis of the 5′*R* and 5′*S* epimers of 6,5′-cyclouridine (1 and **2**, Scheme I). These nucleosides are fixed in the anti conformational range, and the orientations of the 5′-hydroxyl groups correspond approximately to the gauche–trans and trans–gauche $C_{4',5'}$ rotamers, respectively, of unrestricted nucleosides.

In addition to their potential as biochemical tools, 6,5′-cyclonucleosides are interesting from a chemical viewpoint because the allylic character of C-5′ enhances the reactivity of that position relative to ordinary nucleosides. For example, derivatives of **1** and **2** in which the 5′-hydroxyl groups are protected undergo base-catalyzed epimerization at C-5′ via a mechanism involving 5′-carbanion intermediates.[4] We now wish to report that 6,5′-cyclopyrimidine nucleosides with unsubstituted 5′-hydroxyl groups readily undergo base-catalyzed autoxidation and that the resulting 5′-oxo nucleosides can rearrange to give their D-xylo epimers.

The first example of autoxidation of a 6,5′-cyclopyrimidine nucleoside was encountered during the synthesis of inter-

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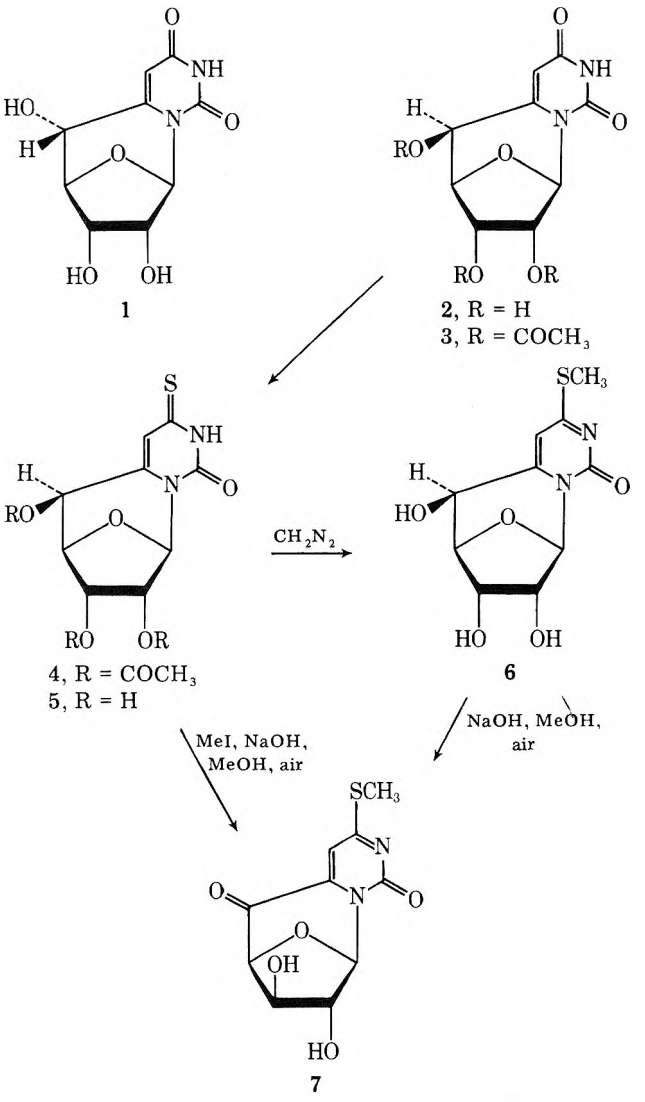
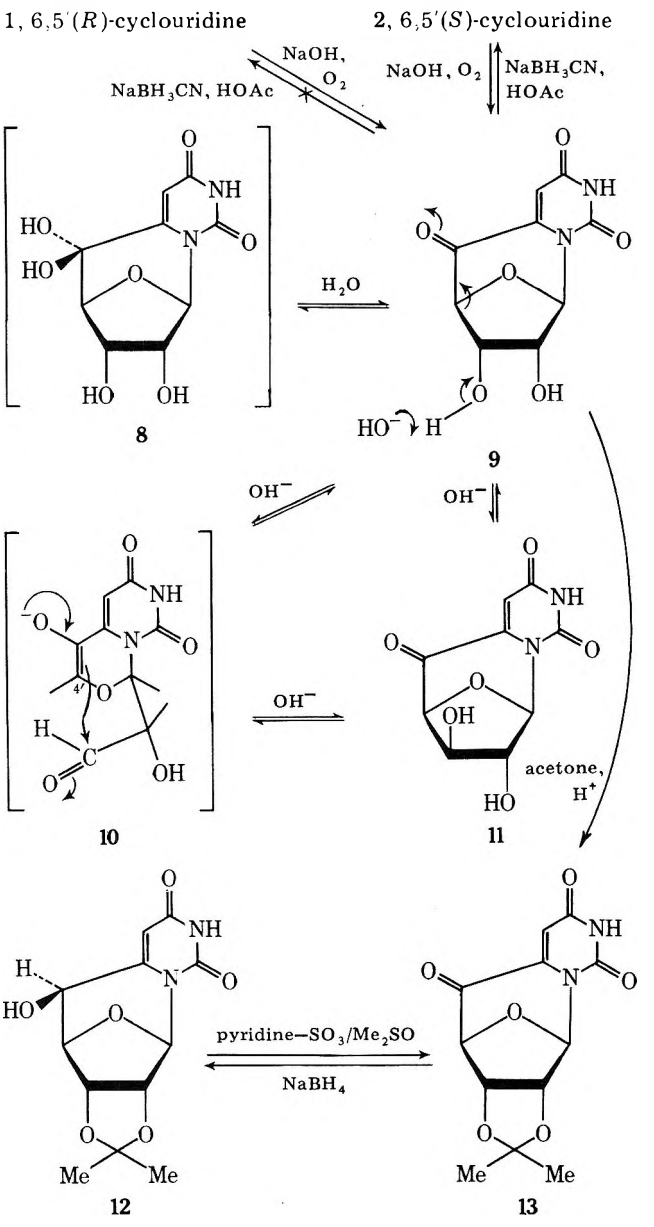
Scheme I



Scheme II



mediates required for the preparation of the 6,5′-cyclocytidine[5] analogues of **1** and **2**. Thus, although methylation of thione **5** with diazomethane affords the expected 4-methylthio nucleoside **6**, methylation of **5** or its tri-*O*-acetate **4** with methyl iodide in aqueous methanol at pH 9 affords, unexpectedly, the 5′-oxo-xylosyl nucleoside **7**. The same product (**7**) is obtained when **6** is treated with aqueous sodium hydroxide in methanol (pH 9), and chromatography indicates that **6** is probably an intermediate in the conversion of **5** into **7**. The structure of **7** and the manner of its formation were deduced from subsequent experiments with the 6,5′-cyclouridines **1** and **2** described below.

6,5′(*S*)-Cyclouridine (**2**) is stable in 1 N NaOH under nitrogen, but it is converted readily into the 5′-oxo-ribo nucleoside **9** in the presence of air or oxygen (Scheme II). Autoxidation of 6,5′(*R*)-cyclouridine (**1**) also affords **9**, indicating that oxidation occurs at the 5′ position. Interestingly, the rate of oxidation of **1** is much slower than that of **2**. That **9** retains the ribo configuration is evident from the NMR spectrum and from the fact that **9** can be converted into an isopropylidene derivative **13**, identical with that obtained by sulfur trioxide–pyridine oxidation[6] of **12**.

The keto nucleoside **9** is stable in 1 N NaOH, in which it is formed from **1** or **2**, but under less strongly alkaline conditions it equilibrates with its 5′-oxo-xylo isomer **11**. This isomerization is very rapid at pH 8–9, where the equilibrium favors the xylo nucleoside **11**, and occurs at an appreciable rate simply on dissolving **9** in water. Preparatively, treatment of **9** with dilute ethanolic ammonia, followed by removal of ammonia by evaporation, affords a mixture from which the major isomer (**11**) crystallizes readily. Compound **11** correspondingly reequilibrates with its ribo isomer **9** on dissolution in water or dilute alkali. NMR studies show that the equilibrium **11** ⇌ **9** in 1 N NaOD lies entirely in favor of the ribo isomer **9**, a finding that explains the apparent stability of **9** in 1 N NaOH.

The sequence of events occurring in the conversion of **4** into **7** (Scheme I) is therefore S-methylation to give **6**, followed by autoxidation to give the 5′-oxo analogue of **6**, which equilibrates with the observed xylo product **7** under the mild conditions used (pH 9).

The assignment of the xylo configuration to **7** and **11** rests on their NMR (Me_2SO-d_6), which show $J_{3',4'}$ values of 7.4 Hz and very small values (<0.5 Hz) for $J_{2',3'}$ (Table I). In contrast, the ribo epimer **9** shows $J_{3',4'} = 0$ and $J_{2',3'} = 6.3$ Hz. Similar differences were observed in the NMR spectra of the phenylhydrazones of **9** and **11**. Additionally, both **7** and **11** show long-range coupling (1.2 Hz) between H-1′ and H-3′, which is consistent with the geometry of the xylo configuration. Four-bond couplings of similar magnitude have been observed previously for a variety of bicyclic carbohydrates.[7]

The most likely mechanism for the interconversion of **9** and **11** is a retro-aldol cleavage to generate the pyrimido[1,6-c]-

Table I. First-Order Coupling Constants,[a] Hz

Compd	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{1',3'}$	$J_{5,5'}$	$J_{5,NH}$	$J_{5',5'OH}$	$J_{3',3'OH}$	$J_{2',2'OH}$
3	6.1	0	6.4	0	1.3	1.3			
4	6.2	0	6.2	0	1.3	1.3			
5	6.1	0	6.1	0	1.2	1.2	6.1	7.0	5.5
6	6.1	0	6.1	0	1.2		6.1	7.0	5.5
9[b,c]	6.3	0		0		2.1		*d*	*d*
9 (**8**)	6.1	0		0		ex	ex	ex	ex
9X[l]	6.4	0		0		1.8		6.4	5.5
7[e]	~0.5[f]	7.4		1.2				4.5	4.3
11[b]	~0.5[f]	7.4		1.2		*g*		4.4	4.3
11X[l]	1.2	6.7		1.2		1.1		*k*	5.2
16 (NaOD)[e,i]	~0.5[f]	6.6	5.9	1.2	1.2	ex	ex	ex	ex
14	~1.0[f]	7.3	~0.5	1.2[j]	~0.5	*k*	6.7	4.0	4.9
15[b]	0	6.4	6.1	1.1	1.2	2.0			4.3

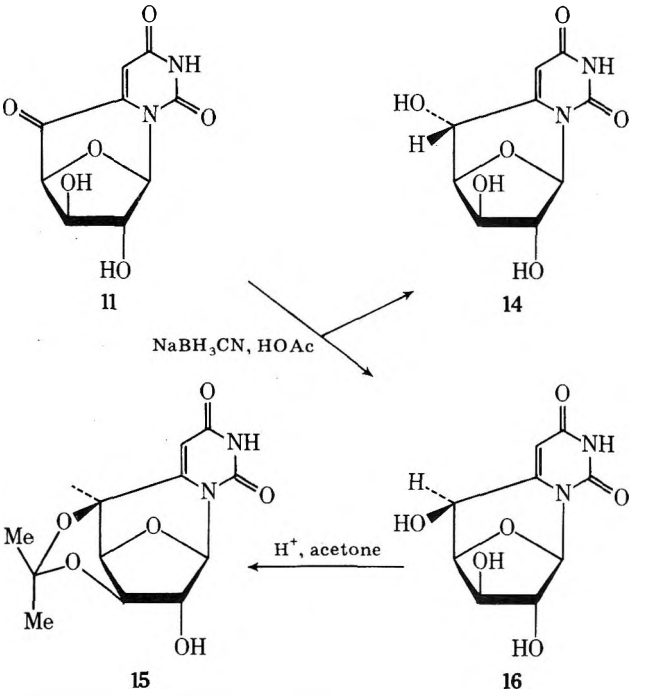
[a] In all cases $J_{1',2'} = 0$ Hz. Values for $J_{2',3'}$, $J_{3',4'}$, and $J_{4',5'}$ for compounds with unsubstituted hydroxyl groups were obtained after addition of D_2O. Computer resolution = 0.3 Hz unless stated otherwise. [b] Computer resolution = 0.15 Hz. [c] $^4J_{1',4'} = 0.76 \pm 0.15$ Hz. [d] First-order values not obtainable. [e] Computer resolution = 0.19 Hz. [f] $J_{2',3'}$ not resolved but detectable by decoupling. [g] Obscured by 2′-OH signal but detectable by decoupling. [h] Obscured by H-1′ and H-4′ signals. [i] $^4J_{3',5'} = 1.2 \pm 0.19$ Hz. The only first-order values obtainable for **16** in Me_2SO-d_6 are $J_{2',2'OH} = 4.5$ Hz and $J_{3',3'OH} = 4.0$ Hz. [j] Obtained after D_2O addition and decoupling $J_{2',3'}$. [k] Obscured by H-1′ signal. [l] Phenylhydrazone derivative.

[1,3]oxazine intermediate **10**, which can then recyclize to give either **9** or **11** depending on the orientation of the aldehyde group in the transition state. The rate of ring closure apparently exceeds the rate at which enolate **10** ketonizes because NMR studies of the **9** ⇌ **11** interconversion under a variety of alkaline conditions in D_2O show that deuterium is not incorporated at C-4′ of either **9** or **11**. Lack of deuterium incorporation, however, rules out the possibility that the 3′ epimerization involves abstraction of H-4′ and elimination of the 3′-hydroxyl group, followed by rehydration. This dehydration–rehydration sequence is in any case unlikely because formation of the olefinic intermediate would violate Bredt's rule. Further support for the retro-aldol mechanism comes from the fact that the isopropylidene nucleoside **13**, in which the 3′-hydroxy group is blocked, is stable to conditions that promote rapid equilibration of **9** and **11**.

A C-3′ epimerization reaction similar to that described above was observed recently by Youssefyeh et al.[8] during the base-catalyzed aldol coupling of formaldehyde with unprotected uridine 5′-aldehyde. Their reaction involves hydroxymethylation at C-4′ of uridine 5′-aldehyde, followed by Cannizzaro reduction of the original 5′-aldehyde group to give 4′-hydroxymethyluridine, together with its 3′ epimer.[9] These authors[8] also suggested a retro-aldol–aldol cyclization mechanism, and our results with the nonenolizable, constrained ketones **9** and **11** tend to support this proposal.

A curious feature of the retro-aldol equilibration of **9** and **11** is that the reaction itself, and the purity of individual preparations of **9** and **11**, can be monitored by UV spectroscopy. This follows from the finding that ribonucleoside **9** is largely hydrated in water and has a UV spectrum different from that of xylo nucleoside **11**, which exists in water in the keto form. In water, compound **9** absorbs strongly at 270 nm but shows a much smaller peak at 315 nm. In contrast, nucleoside **11** absorbs strongly at 312 nm and has no discrete peak at 270 nm. Removal of the 5′-carbonyl conjugation by hydration would be expected to result in a hypsochromic shift, and the 270-nm absorption of **9** can therefore be attributed to the hydrate **8**. In support of this conclusion, it should be noted that solutions of **9** in anhydrous dioxane absorb *only* at 321.5 nm but that addition of water to the dioxane solution results in the reappearance of absorption at 270 nm.[10] Further evidence for the existence of **8** comes from NMR studies of **9** in aqueous systems. Thus, the NMR spectrum of **9** in Me_2SO-d_6 consists of a single set of peaks (Table II), but addition of D_2O results in the gradual appearance of an additional set of peaks, attributable to **8**, which reach a constant 8/9 ratio of ~1:1. Similarly, the NMR spectrum of **9** in D_2O alone shows *two* sets of peaks, with a 8/9 ratio of 3.5:1. On the other hand, xylo nucleoside **11** gives a *single* set of peaks in D_2O and Me_2SO-d_6–D_2O that is closely similar to the spectrum in anhydrous Me_2SO-d_6, indicating in this case that the equilibrium lies heavily in favor of the keto form of **11**.

Scheme III



A further instance where the ribo (**9**) and xylo (**11**) 5′-keto nucleosides show disparate properties concerns their reduction with sodium cyanoborohydride in acetic acid. This reagent combination[11] (pH ~4) was used because alkaline solutions of sodium borohydride induce C-3′ epimerization, with consequent formation of mixtures of ribo- and xylo-6,5′-cyclopyrimidine nucleosides. Cyanoborohydride reduction of **9** gives 6,5′(*S*)-cyclouridine (**2**), with no detectable formation of the 5′*R* isomer **1**. Similar reduction of **11**, however, affords both the 5′*R* and 5′*S* isomers of 6,5′-cyclo-1-(β-D-xylofuranosyl)uracil (**14** and **16**, respectively, Scheme III) in a ratio of 1:5. Clearly, attack by the cyanoborohydride ion on **9** and **11** occurs in both cases primarily from the less hindered, rear side

Table II. Proton Chemical Shifts (δ) at 100 MHz[a]

Compd	Registry no.	N_3H	C_5H	$C_1'H$	$C_2'H^b$	$C_3'H^b$	$C_4'H$	$C_5'H$	$O_5'H$	$O_2'H^b$	$O_3'H^b$	Other
3	64200-89-1	11.41	6.06 n m	5.74	5.41 d	5.60 d	4.72 d	5.82 dd				OAc 2.02, 2.12, 2.15
4	64200-88-0	12.76	6.39 t	5.76	5.44 d	5.61 d	4.74 d	5.76 dd				OAc 2.02, 2.12, 2.15
5	64200-87-9	12.63	6.39 n m	5.73	4.11 t	4.35 t	4.26 d	4.64 dt	6.51 d	5.40 d	5.26 d	
6	64200-86-8		6.51 d	5.78	3.99 t	4.35 t	4.28 d	4.75 dt	6.51 d	5.48 d	5.22 d	SMe 2.44
9[c]	64234-75-9	11.74	6.12 d	5.93	——— 4.34 m ———		4.67			——— 5.61 d ———		
9 (8)[d]	64200-83-5	ex	5.88	5.74	3.99 d	~4.3 d	4.06			ex	ex	
9X[e]	64234-74-8	11.25	6.05 d	5.93	4.15 dd	4.30 t	5.62			5.33	5.68	PhNH 10.66, Ph (4 H, m) 7.30, (1 H, m) 6.95
13	64200-82-4	11.84	6.15 d	6.07	———	4.97 ———						Ip 1.44, 1.29
7	64200-81-3		6.87	5.85 d	4.07 d	4.48 m	5.15 d			6.19 d	6.24 d	SMe 2.50
11	64200-80-2	11.79	6.08 d	5.81 d	4.08 d	4.46 m	5.09 d			6.09 d	6.22 d	
11X[f]	64200-79-9	11.29	6.15 d	~5.77 d	3.94 dd	4.35 m	~5.74 d			6.00 d	~5.77 d	PhNH 10.37, Ph (4 H, m) 7.29, (1 H, m) 6.95
16	64234-73-7	11.33	———	5.63 m ———		3.89 d	4.41 m	4.65 m	4.95 m	5.86 d	6.03 d	
16[g]		ex	5.85 d	5.77 d		4.08 d	4.51 m	4.67 dd 4.93 dt	ex	ex	ex	
14	64234-72-6	11.34	———	5.61 m ———		3.72 d	4.18 m	4.56 d 4.44 d	6.07 d	5.81 d	5.69 d	Ip 1.24, 1.38
15	64200-78-8	11.39	5.57 dd	5.76 d	4.04 d	4.46 dd	5.05 t	4.86 dd		6.08 d		

[a] Spectra were obtained on a JEOL PFT-100 spectrometer operating in the Fourier transform mode (EC-100 computer) with an internal field frequency lock. Values given for chemical shifts are first order and (except for the N_3H signals of **4** and **5**) were obtained at 1250-Hz width with 8K data points, giving a computer resolution of 0.3 Hz. Unless otherwise stated, Me_2SO-d_6 was used as a solvent with Me_4Si as an internal standard. Peaks are singlets unless designated d (doublet), m (multiplet) dd (doublet of doublets), t (double doublets where coincidence of inner lines gives appearance of triplet), dt (double triplet or ddd), n (Narrow), or ex (exchanged). [b] The assignments of $C_2'H$–$O_2'H$ and $C_3'H$–$O_3'H$ can be interchanged for the ribosyl compounds (first eight entries) since the observed $J_{1',2'} = J_{3',4'} = 0$ Hz precludes unambiguous assignment. [c] Addition of D_2O reveals $C_2'H$ and $C_3'H$ as an AB quartet at δ 4.30 and 4.41. [d] Shifts for hydrated **9** (**8**) in Me,SO-d_6–D,O. [e] Phenylhydrazone derivative of **9**. [f] Phenylhydrazone derivative of **11**. [g] In 1 N NaOD, DSS standard.

of C-5′ to give the 5′*S* products. That reduction of **11** affords appreciable amounts of the 5′*R* isomer **14,** whereas **9,** which is less sterically congested than **11,** affords none of the 5′*R* isomer **1,** may indicate that **14** is formed via participation of the 3′-hydroxyl group rather than by direct cyanoborohydride attack on the more hindered, front face of the 5′-carbonyl group. Thus, the initial reaction of the cyanoborohydride ion with the 3′-hydroxyl group of **11** would form a complex favorably located for delivery of a hydride ion to the front face of the 5′-carbonyl group. A similar explanation has been used previously to account for the stereochemistry of the products obtained from lithium aluminum hydride reduction of cyclic hydroxy ketones.[12]

Assignments of the 5′ configurations to **14** and **16** follow from their respective $J_{4',5'}$ values of <0.5 and 5.9 Hz. These values are diagnostic because Dreiding models show a 4′,5′ dihedral angle of ~90° for **14** and 30° for **16.** Both **14** and **16** show $^4J_{1',3'}$ values of 1.2 Hz, consistent with the xylosyl configuration, and **16** shows an additional four-bond coupling (1.2 Hz) between $H_{3'}$ and $H_{5'}$ that is consistent only with the 5′*S* configuration. Chemical proof of the 5′*S* configuration follows from the finding that **16** readily forms a 3′,5′-*O*-isopropylidene derivative **15,** whereas **14** is inert to acetone and *p*-toluenesulfonic acid because isopropylidene ring formation is sterically impossible. Compound **15,** in which the 2′-hydroxyl group is conveniently unblocked, is expected to be a versatile intermediate in further studies involving transformations of the sugar rings of these 6,5′-cyclopyrimidine nucleosides. We also anticipate that the retro-aldol C-3′ epimerization reaction will be applicable to other cyclonucleosides, e.g., 8,5′-cyclopurine nucleosides, of interest as probes of conformational aspects of enzyme–substrate interactions.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were measured on Cary Model 15 and Varian Superscan 3 spectrometers and infrared spectra (KBr disk) were obtained with a Perkin-Elmer Infracord. Thin-layer chromatography was performed on 1 × 3 in. microscope slides coated with silica gel GF_{254} (Merck) and preparative separations were effected on 20 × 20 cm, 1-mm silica gel GF plates (Analabs Inc.). Separated materials were detected with ultraviolet light and/or by spraying with sulfuric acid in ethanol (10% v/v) followed by charring. Evaporations were carried out in vacuo with bath temperatures kept below 45 °C. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

2′,3′,5′-Tri-*O*-acetyl-6,5′(*S*)-cyclouridine (3).[13] 2′,3′-*O*-Isopropylidene-6,5′(*S*)-cyclouridine[4] (**12,** 1.18 g, 4.2 mmol) was dissolved with stirring in 80% acetic acid (40 mL), and the solution was refluxed for 8 h, at which time TLC (EtOAc) showed complete absence of starting material. The solution was concentrated to dryness, and pyridine (2 × 25 mL) was added to and evaporated from the residue. The final crystalline residue, comprising mostly 6,5′(*S*)-cyclouridine (**2**) together with small amounts of partially acetylated material, was dissolved in a mixture of pyridine (25 mL) and acetic anhydride (5 mL, 53 mmol). After 2 h at room temperature (TLC, EtOAc), ethanol was added to hydrolize excess acetic anhydride, and the mixture was evaporated to dryness. A solution of the residue in chloroform was washed with cadmium chloride solution to remove traces of pyridine. The organic layer was filtered, washed with water, and dried over sodium sulfate. Removal of the solvent afforded a dry foam which crystallized readily from warm ethanol to give 1.2 g (78%, TLC pure) of **3,** mp 209–210 °C.

Anal. Calcd for $C_{15}H_{16}N_2O_9$ (mol wt 368.30): C, 48.92; H, 4.38; N, 7.61. Found: C, 48.78; H, 4.40; N, 7.68.

2′,3′,5′-Tri-*O*-acetyl-6,5′(*S*)-cyclo-4-thiouridine (4). Phosphorus pentasulfide (1.0 g, 4.5 mmol) was added to a solution of **3** (1.0 g, 2.7 mmol) in 40 mL of dioxane, and the mixture was refluxed for 2 h (TLC, EtOAc/petroleum ether (30–60 °C), 1:1). The cooled mixture was filtered, and the filtrate and washings were concentrated to dryness. The solid residue was partitioned between dichloromethane and water; the organic layer was washed with water, dried over sodium sulfate, and evaporated to dryness. A solution of the residue in ~30

Table III. UV Data for 5′-Oxo-6,5′-cyclouridine (9)

Solvent	λ_{max} (ϵ)	λ_{max} (ϵ)	λ_{min} (ϵ)
Dioxane	321.5 (5460)		~250–280 (1540)
80% dioxane	321.5 (3750)	270 (4210)	295.5 (2420)
20% dioxane	318.5 (1670)	270 (7125)	299.5 (1300)
0.1 N HCl	315 (1420)	270 (8950)	300 (1240), 233 (1360)

mL of hot ethanol deposited 960 mg (92%) of **4** (yellow needles, TLC pure): mp 194–196 °C; UV λ_{max} (H_2O) 334, 279, 252 nm, λ_{min} 289, 262 nm.

Anal. Calcd for $C_{15}H_{16}N_2O_8S$ (mol wt 384.36): C, 46.87; H, 4.20; N, 7.29. Found: C, 46.85; H, 4.22; N, 7.26.

6,5′(*S*)-Cyclo-4-thiouridine (5). Four 1-mL portions of 1 N NaOH (4 mmol) were added over a 10-min period to a suspension of **4** (1.26 g, 3.28 mmol) in 40 mL of methanol. The solution was kept at room temperature for 1.5 h, when TLC (EtOAc) indicated complete hydrolysis. The solution was deionized by passage through excess Dowex 50 (H^+, previously equilibrated with methanol). Crystallization of **5** commenced on concentration of the effluent and was completed by cooling: yield 600 mg (73%); mp 249–250 °C; UV λ_{max} (H_2O) 250, 335 nm, λ_{min} 260 nm; λ_{max} (pH 11) 320, inflection 274–286 nm, λ_{min} 258 nm.

Anal. Calcd for $C_9H_{10}N_2O_5S$ (mol wt 258.25): C, 41.85; H, 3.90; N, 10.85. Found: C, 41.91; H, 3.94; N, 10.90.

6,5′(*S*)-Cyclo-4-methylthiouridine (6). A solution of **5** (400 mg, 1.55 mmol) in hot methanol (75 mL) was cooled rapidly to prevent crystallization. An excess of diazomethane in ether (dried over KOH) was added, and the solution was stored at room temperature until TLC (EtOAc) indicated that the reaction was complete. Removal of the ether and cooling afforded 200 mg (48%) of **6** with good TLC purity. Further crops contained traces of a faster moving component which was not fully characterized but which has an NMR spectrum consistent with the isomeric *N*-methyl compound (N–Me δ 3.56, Me_2SO-d_6). Recrystallization of **6** from methanol afforded pale yellow needles: mp 198–203 °C dec; UV λ_{max} (H_2O) 307, 225–238 (sh), 256–284 (sh), 313–320 nm (sh), λ_{min} 242 nm.

Anal. Calcd for $C_{10}H_{12}N_2O_5S$ (mol wt 272.28): C, 44.11; H, 4.44; N, 10.29. Found: C, 43.93; H, 4.50; N, 10.31.

6,5′-Cyclo-5′-oxo-1-(β-D-xylofuranosyl)-4-methylthiouracil (7). Method A. Methyl iodide (0.2 mL, 3.2 mmol) was added to a solution of **5** (100 mg, 0.39 mmol) in 15 mL of methanol, and the pH was adjusted to and maintained at ~9 by the dropwise addition of 1 N NaOH. TLC (CH_2Cl_2/MeOH, 9:1) at 30 min indicated the disappearance of starting material and the formation of **6**, which in turn was converted into a faster moving component. After 3 h, the reaction mixture was neutralized with acetic acid, the volume was reduced, and the solution was applied to a preparative TLC plate. The plate was developed in CH_2Cl_2/MeOH (9:1), and the major zone was removed and extracted with 50 mL of EtOAc/MeOH (1:1). Concentration of the filtrate afforded pale yellow crystals of **7**: 60 mg (57%); mp 250–253 °C dec, darkens from 244 °C; UV λ_{max} (H_2O) 341, 229, 318–333 nm (sh), λ_{min} 265 nm; IR 1740 cm^{-1} (5′-oxo).

Anal. Calcd for $C_{10}H_{10}N_2O_5S$ (mol wt 270.26): C, 44.44; H, 3.72; N, 10.37. Found: C, 44.21; H, 3.76; N, 10.40.

Method B. A solution of **6** (20 mg) in methanol (1.5 mL) containing ~2 drops of 1 N NaOH was kept at room temperature for 3 h. Isolation of the product by preparative TLC as described above afforded 16 mg (81%) of material, identical (melting point, IR, UV, and NMR) with **7** prepared according to method A.

5′-Oxo-6,5′-cyclouridine (9). Method A. A slow stream of oxygen was passed through a solution of 6,5′(*S*)-cyclouridine (**2**, 500 mg) in 1 N NaOH (25 mL) for 60 h. The solution was neutralized by passage through excess Dowex 50 (H^+), and the effluent and washings (pH ~5) were concentrated to a clear syrup. Crystallization from ethanol afforded two crops of **9** (228 and 79 mg, total yield 62%). The mother liquors contained more **9**, together with xylo isomer **11**. An analytical sample of **9** was obtained by recrystallization from ethanol: mp 220–222 °C, resolidified, ~260 °C[14] dec; IR 1750 cm^{-1} (5′-oxo) (UV, see Table III).

Anal. Calcd for $C_9H_8N_2O_6$ (mol wt 240.17): C, 45.01; H, 3.38; N, 11.66. Found: C, 45.10; H, 3.40; N, 11.78.

Compound **9** readily forms a phenylhydrazone in methanol, mp >300 °C (recrystallized from 10% aqueous EtOH).

Anal. Calcd for $C_{15}H_{14}N_4O_5$ (mol wt 330.30): C, 54.55; H, 4.27; N, 16.96. Found: C, 54.38; H, 4.42; N, 16.74.

Method B. A solution of 6,5′(*S*)-cyclouridine[4] (**2**, 5 mg) in 0.5 mL of 1 N NaOD containing a trace of DSS was oxygenated in an NMR tube at room temperature. The NMR spectrum after 24 h showed complete conversion into **9** (hydrate), which shows signals at δ 5.97 (1, s, H-5), 5.83 (1, s, H-1′), 4.19 (1, d, H-3′, $J_{2',3'}$ = 6.1 Hz), and 3.98 (2, H-2′ d overlapping H-4′ s). This spectrum is identical with that of crystalline **9** in 1 N NaOD.

The above experiment was repeated on the same scale and under identical conditions with 6,5′(*R*)-cyclouridine[4] (**1**). The oxidation was considerably slower; after 92 h, integration indicated a **1**/**9** (hydrate) ratio of 3.2:1, with the signals for **9** (hydrate) (H-3′ obscured by H-4′ and H-5′ of **1**) identical with those above.

6,5′-Cyclo-5′-oxo-1-(β-D-xylofuranosyl)uracil (11). Method A. An aqueous ammonia solution (1 mL, 1 N) was added to a solution of **9** (80 mg) in warm ethanol (10 mL). The volume was reduced to 2 mL, and the solution was refrigerated, affording 47 mg (59%) of **11** (prisms): mp 260 °C dec, darkens above 240 °C; IR 1750 cm^{-1} (5′-oxo); UV λ_{max} (0.2 N HCl) 312 nm (ϵ 6200), λ_{min} 250 nm (ϵ 1485); λ_{max} (dioxane) 315 nm, λ_{min} 262 nm.

Anal. Calcd for $C_9H_8N_2O_6$ (mol wt 240.17): C, 45.01; H, 3.38; N, 11.66. Found: C, 44.88; H, 3.38; N, 11.64.

The mother liquors contained both **9** and **11**. Further crops of **11** can be obtained by treating the residue with ethanolic ammonia as above, followed by concentration and cooling of the solution.

Method B. 6,5′(*S*)-Cyclouridine[4] (**2**, 500 mg) was oxidized in 1 N NaOH as described above (method A) for the preparation of **9**. The clear syrup, obtained after evaporation of the deionized reaction mixture, was dissolved in 50 mL of ethanol. A 5-mL amount of a 1 N ammonia solution was added, and the solution was concentrated to ~10 mL and cooled. Crystalline **11** (279 mg) was collected; additional crops of 51 and 45 mg (total yield 75%) were obtained by retreating the residues with ethanolic ammonia. Compound **11** reisomerizes in 1 N NaOD to give ribonucleoside **9**, as shown by the change of the NMR spectrum [**11** (D_2O) δ 6.49 (s, H-5), 6.09 (d, H-1′, $J_{1',3'}$ = 1.2 Hz), 5.23 (d, H-4′, $J_{3',4'}$ = 7.6 Hz), 4.65 (dd, H-3′), 4.38 (s, H-2′)] to that described above for **9** (hydrate), preparation B.

Compound **11** forms a crystalline phenylhydrazone in 50% acetic acid, mp 275–280 °C dec, darkens above 265 °C (recrystallized from H_2O).

Anal. Calcd for $C_{15}H_{14}N_4O_5 \cdot H_2O$: C, 51.72; H, 4.63; N, 16.09. Found: C, 52.13; H, 4.28; N, 16.15.

2′,3′-*O*-Isopropylidene-5′-oxo-6,5′-cyclouridine (13). Method A. A suspension of **9** (55 mg) in acetone (3 mL) containing *p*-toluenesulfonic acid hydrate (15 mg) and 2,2-dimethoxypropane (0.1 mL) was stirred rapidly at room temperature. Further additions of dimethoxypropane (0.1 mL) were made after 1 and 3 h; TLC (EtOAc) indicated an essentially complete reaction after 4 h. The reaction mixture was neutralized by the addition of a saturated sodium bicarbonate solution, and the volume was reduced to ~0.5 mL. Crystalline **13** (34 mg, 53%) formed on the addition of water. The analytical sample was recrystallized from EtOAc/petroleum ether (bp 30–60 °C): mp 225–226 °C; UV λ_{max} (H_2O) 268, 316 nm, 268/316 = 7.0, λ_{min} 236, 298 nm, λ_{max} (dioxane) 320 nm, λ_{min} 268 nm, 268/316 = 0.34.

Anal. Calcd for $C_{12}H_{12}N_2O_6$ (mol wt 280.24): C, 51.43; H, 4.31; N, 10.00. Found: C, 51.16; H, 4.35; N, 9.80.

Method B. A solution of the sulfur trioxide–pyridine complex (477 mg, 3 mmol) in Me_2SO (1 mL) was added to a solution of **12** (282 mg, 1 mmol) in Me_2SO (1 mL) containing triethylamine (1 mL, 7 mmol), and the mixture was stored at room temperature for 17 h. The solution was acidified with glacial acetic acid and evaporated to dryness (lyophilization). Water was added to the residue, and crystalline starting material (**12**, 40 mg; TLC; NMR) was removed. The filtrate, which contains **13** and **12** as the main components, was applied to a preparative TLC plate. Development in benzene/ethyl acetate (1:2), followed by extraction of the appropriate zone with EtOAc and concentration to dryness, afforded pure **13** (95 mg) with melting point and IR, UV, and NMR spectra identical with **13** prepared as above. No attempt was made to optimize the yield of **13**.

Reduction of **13** (20 mg, 0.08 mmol) in methanol (5 mL) containing sodium borohydride (0.7 mL of a 1 N aqueous solution) for 30 min afforded a solution containing **12**, together with some faster moving (TLC, EtOAc) fluorescent materials. The identity of **12**, purified by preparative TLC, was established by comparison of the NMR spectrum with that of authentic material.[4]

6,5′(*S*)-Cyclouridine (2). Sodium cyanoborohydride (10 mg, 0.16 mmol) was added to a solution of **9** (36 mg, 0.15 mmol) in a mixture of methanol (2 mL) and acetic acid (0.5 mL). The solution was stored at room temperature for 1 h (TLC, EtOAc, dinitrophenylhydrazine spray) and then concentrated to dryness. An aqueous solution of the residue was passed through excess Dowex 50 (H^+), the eluate was evaporated to dryness, and methanol was repeatedly evaporated from the crystalline residue. The NMR spectrum (Me_2SO-d_6) of the re-

sulting crystalline mass (35 mg, 96%) was identical with that of authentic **2**;[4] none of the 5′*R* isomer **1** was detected, even with the very high signal-to-noise ratio resulting from prolonged spectral accumulation.

6,5′(*S*)-Cyclo-1-(β-D-xylofuranosyl)uracil (16) and 6,5′(*R*)-Cyclo-1-(β-D-xylofuranosyl)uracil (14). Sodium cyanoborohydride (40 mg, 0.64 mmol) was added to a suspension of **11** (150 mg, 0.53 mmol) in a mixture of water, acetic acid, and methanol (1:1:1, 6 mL). The mixture was stirred and warmed briefly to ~40 °C to effect dissolution and then cooled to room temperature. The reduction was monitored by the disappearance of the 310-nm peak of **11** and the appearance of absorption at 268 nm, a process that was complete after ~3.5 h. The solution was deionized by passage through an excess of Dowex 50 (H^+), the eluate and washings were concentrated to dryness, and methanol was repeatedly evaporated from the residue. The NMR spectrum (Me_2SO-d_6) of the residue showed compounds **14**/**16** in a ratio of 1:5. Pure **14** (80 mg) was obtained by crystallization of the residue from hot 80% ethanol: mp 246–248 °C; UV λ_{max} (H_2O) 268 nm, λ_{min} 233 nm; λ_{max} (pH 9) 266 nm, λ_{min} 241 nm.

Anal. Calcd for $C_9H_{10}N_2O_6$ (mol wt 242.19): C, 44.63; H, 4.16; N, 11.57. Found: C, 44.56; H, 4.14; N, 11.47.

A further sample of **14** (30 mg) and pure **16** (10 mg) was obtained by fractionation of the residue by preparative TLC (CH_2Cl_2/MeOH, 8:1; triple development). Compound **16** crystallized from aqueous ethanol: mp 250–253 °C dec, darkens and shrinks above 230 °C; UV λ_{max} (H_2O) 271 nm, λ_{min} 237 nm; λ_{max} (pH 10) 270 nm, λ_{min} 245 nm.

Anal. Calcd for $C_9H_{10}N_2O_6$ (mol wt 242.19): C, 44.63; H, 4.16; N, 11.57. Found: C, 44.86; H, 4.14; N, 11.36.

6,5′(*S*)-Cyclo-3′,5′-*O*-isopropylidine-1-β-D-xylofuranosyl)-uracil (15). A suspension of **16** (54 mg, 0.22 mmol) in acetone (3 mL) containing 15 mg of *p*-toluenesulfonic acid monohydrate and 0.1 mL of 2,2-dimethoxypropane was stirred rapidly at room temperature. The slow dissolution of **16** (~1 h) was followed by the appearance of crystalline **15**. After 3 h, the crystals (27 mg) were removed and washed with cold acetone. The filtrate was diluted with 0.1 mL of water, solid sodium bicarbonate was added, and the mixture was filtered. The filtrate was evaporated to dryness, and a solution of the residue in methanol was applied to a preparative TLC plate. After development (EtOAc), the appropriate zone was removed, the silica was extracted with ethyl acetate, and the filtrate was concentrated to dryness. Crystallization from 90% acetone afforded 20 mg (total yield 75%) of **15**: mp 265–266 °C, UV λ_{max} (H_2O) 269.5 nm, λ_{min} 233 nm; λ_{max} (pH 10) 270 nm, λ_{min} 243 nm.

Anal. Calcd for $C_{12}H_{14}N_2O_6$ (mol wt 282.25): C, 51.07; H, 5.00; N, 9.93. Found: C, 51.24; H, 5.05; N, 9.89.

Registry No.—**1**, 59728-02-8; **2**, 59686-60-1; **12**, 59686-58-7; acetic acid, 64-19-7; diazomethane, 334-88-3; methyl iodide, 74-88-4; phenylhydrazide, 100-63-0; 2,2-dimethoxypropane, 77-76-9.

References and Notes

(1) This investigation was supported by funds from the American Cancer Society (Grant CH-38) and from the National Institute of Health, U.S. Public Health Service (Grant No. 17085, for NMR studies).

(2) This paper is the second in a series entitled Conformationally Restricted Analogues of Pyrimidine Nucleosides. For Part 1, see ref 4.

(3) Reviews that stress the relationship between nucleoside–nucleotide conformation and biological activity include the following: (a) D. C. Ward and E. Reich, *Annu. Rep. Med. Chem.*, 272 (1969); (b) W. Saenger, *Angew. Chem., Int. Ed. Engl.*, **12**, 591 (1973). For examples of the use of conformationally restricted nucleotides to investigate enzyme specificity see the following: (a) A. Hampton, P. J. Harper, and T. Sakai, *Biochemistry*, **11**, 4965 (1972); (b) A. Matsuda, M. Tezuka, and T. Ueda, *Nucleic Acids Res., Spec. Publ.*, **No. 2**, S 13 (1976); (c) J. Zemlicka, *J. Am. Chem. Soc.*, **97**, 5896 (1975).

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(5) The synthesis of 6,5′(*S*)- and 6,5′(*R*)-cyclocytidine will be reported in a subsequent paper.

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(9) It is not clear whether the C-3′ epimerization precedes or follows hydroxymethylation at C-4′ because the stability of uridine 5′-aldehyde alone in base was not reported. In either case, four initial products are possible since C-4′ can also epimerize, but this number is reduced to two (C-3′ epimers) because the subsequent Cannizzaro reaction removes the C-4′ asymmetry.

(10) Carbonyl hydration, and its effect on the UV spectrum, may be a common feature of 6-acylpyrimidines. Thus orotaldehyde (uracil 6-carboxaldehyde) absorbs in water (pH 1) at 261 nm (ε 8200), but it also shows a small shoulder at 300 nm (ε 700). On the basis of the above results, the 261-nm peak represents hydrated orotaldehyde, and the 300-nm peak can be attributed to the anhydrous form. In dioxane, orotaldehyde absorbs only at 300 nm. The literature value [K.-Y. Zee-Cheng and C. C. Cheng, *J. Heterocycl. Chem.*, **4**, 163 (1967)] for orotaldehyde is λ_{max} (pH 1–7) 261 nm (ε 13 300), with no mention of 200-nm absorption. We could not reproduce the ε 13 300 value, but we feel that our figure of ε 8200 is more in line with the value reported by the same authors for thymine 6-carboxaldehyde (ε 7800). In MeSO-d_6, anhydrous orotaldehyde shows NMR signals at δ 9.56 (s, CHO) and 6.28 (dd, H-5, $J_{N_3H,5} = J_{N_1H,5} = 1.8$ Hz). In D_2O, the anhydrous form [δ 9.60 (s, CHO), δ 6.49 (s, H-5)] and the hydrated form [δ 5.92 (d, H-5, $J_{allylic} = 1$ Hz), δ 5.75 (d CH(OD)$_2$)] are present in a ratio of ~1:15.

(11) B. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

(12) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, New York, N.Y., 1972, pp 58–59.

(13) All of the compounds described can be named as substituted 6,9-epoxypyrimido[1,6-*a*]azepines, but for ease of comparison with ordinary nucleosides we prefer the trivial 6,5′-cyclonucleoside designations used herein.

(14) The melting point depends on the rate of heating. Examination of the UV spectrum of the resolidified melt shows that partial rearrangement to xylo isomer **11** occurs. Similarly, *aged* solutions of **9** in Me_2SO-d_6–D_2O rearrange to **11** on heating. In both cases, the reaction is probably catalyzed by alkali leached from the glass.

A Serendipitous Synthesis of 1,2,5,6-Tetramethyl-3,4,7,8-tetramethylenetricyclo[3.3.0.0^{2,6}]octane

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Received May 20, 1977

The title compound (**5**) can be prepared by photosensitized dimerization of 1,2-dimethyl-3,4-dimethylenecyclobutene (**1**) to *anti*-1,2,5,6-tetramethyl-3,4,7,8-tetramethylenetricyclo[4.2.0.0^{2,6}]octane (**2**), followed by flow system pyrolysis of **2** at 380 °C. At lower temperatures an intermediate, 1,2,5,6-tetramethyl-3,4,7,8-tetramethylenecycloocta-1,5-diene (**3**), can be isolated. On direct or sensitized photolysis of **3**, **5** is also obtained. The photochemistry of **2** has been explored, and its fragmentation to **1** on direct irradiation is discussed. The photosensitized dimerization of **1** to **2** is also discussed and interpreted in favor of a frontier orbital model for predicting the products of such reactions.

As an intermediate in a proposed synthesis, we required 1,2:5,6-bis(ethano)cyclooctatetraene (**4**, R = H) or a simple derivative thereof. Attempts to convert 1,2:5,6-bis(ethano)-cycloocta-1,5-diene[2] to the tetraene proved fruitless, and so we investigated the route to **4**, R = CH_3, shown in Scheme I. Our synthesis began with the photochemical dimerization of

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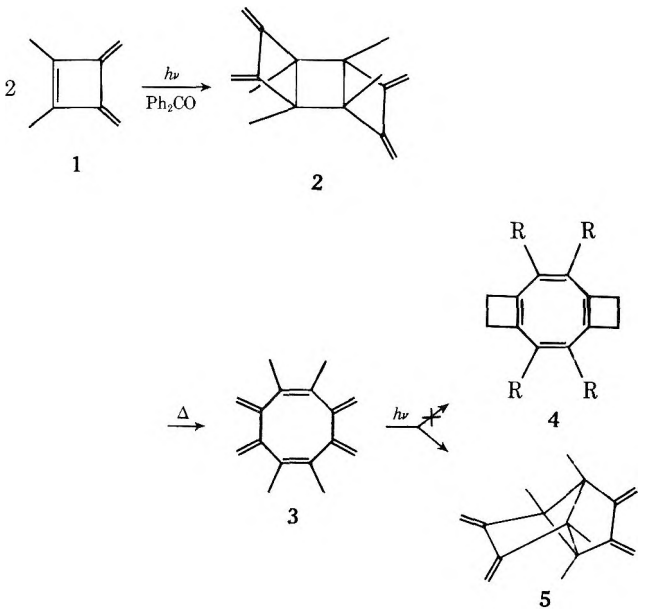
Scheme I

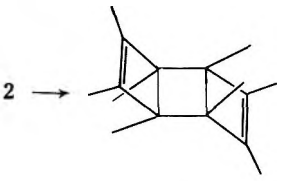


1,2-dimethyl-3,4-dimethylenecyclobutene (1).[3] Although this step and the next—the thermal cleavage of the photodimer (2) to 1,2,5,6-tetramethyl-3,4,7,8-tetramethylenecycloocta-1,5-diene (3)—both proceeded successfully,[4] photolysis of 3 gave, instead of 4, 1,2,5,6-tetramethyl-3,4,7,8-tetramethylenetricyclo[3.3.0.0^{2,6}]octane (5). While the failure of the last step precluded the utilization of Scheme I for the preparation of 4, this route did afford a serendipitous synthesis of 5, a compound whose chemistry[5] was to provide the key to understanding the chemical consequences of orbital interactions in compounds containing unsaturatively 1,3-bridged cyclobutane rings.[6] We report herein details of this synthesis of 5 and discuss the thermal and photochemical behavior of the intermediates.

Results and Discussion

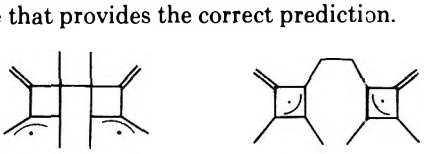
It was with some trepidation that we carried out the photosensitized dimerization of 1, since there are a total of nine products that might be reasonably expected to result from this reaction. Indeed, in the sensitized irradiation of 1,2-dimethylenecyclobutane three of the four possible dimers are obtained as primary photoproducts and the fourth is formed as the result of a Cope rearrangement of one of these, when purification of the dimer mixture by GLC is attempted.[2] However, the HOMO and, since 1 is an AH,[7] the LUMO of 1 both have coefficients of the largest magnitude at C-1 and C-2. Thus, it seemed reasonable to expect that upon sensitized photolysis of 1 the excitation would be localized principally at these atoms of the ring, rather than in the exocyclic double bonds. Moreover, frontier molecular orbital theory predicts ground state 1 to be most readily attacked at these ring carbons, again because both the HOMO and LUMO have coefficients of the largest magnitude at these atoms.[8] Therefore, there was some reason to hope that the photodimerization of 1 might be regioselective and lead principally to 2 or to its syn stereoisomer.

In the event, when 1 was irradiated through Pyrex in a benzene solution, containing sufficient benzophenone to absorb 99% of the light, a single dimeric product was obtained after chromatography of the crude photolysate over alumina. The ^{1}H NMR spectrum of the crystalline product showed four equivalent methyl groups and four equivalent vinyl groups, thus indicating the gross structure 2 for the dimer. The stereochemistry was established as anti by reduction of the dimer to *anti*-octamethyltricyclo[4.2.0.0^{2,5}]octadiene (6), a reaction which could be carried out either by hydrogenation over a 5% Pd/C catalyst[9] or with lithium in ammonia–tetrahydrofuran–*tert*-butyl alcohol. The melting point (125 °C) of the reduction product was in good agreement with that (127 °C) reported for the *anti*-octamethyltricyclooctadiene (6)[10a] but not with that (196 °C) of the syn isomer.[10b] The ^{1}H NMR spectrum of the reduction product in $CDCl_3$ showed two singlets of equal area at δ 0.91 and 1.56, in excellent agreement with the spectrum of an authentic sample of 6,[10c] but different from that of the syn compound (δ 0.99 and 1.49), which we prepared by the literature procedure[10b] for comparison.



6

The structure of the photodimer (2) formed on sensitized irradiation of 1 is of some theoretical interest, for despite the steric hindrance afforded by the methyl groups attached to the endocyclic double bond of 1, the gross structure of 2 is in accord with the prediction based on analysis of the frontier MO's of 1. Usually, however, the products of sensitized photodimerization reactions are rationalized by the principle of formation of the most stable diradical intermediate.[11] For instance, in the sensitized photodimerization of dienes the most stable diradical is that which results from bonding between the terminal atoms of the excited triplet and the ground state diene. However, the formation of the same diradical is predicted by frontier orbital analysis, since the HOMO and LUMO of a diene have their largest coefficients at the terminal atoms. Although frontier orbital analysis and the principle of formation of the most stable diradical make the same prediction regarding the intermediate initially created by the sensitized photolysis of dienes (and, more generally, of linearly conjugated polyenes), these two models differ in their prediction of the diradical involved in the photosensitized dimerization of 1. As noted above, frontier orbital analysis predicts 7 to be the diradical intermediate in this reaction, while the more stable diradical is 8.[12] Thus, this reaction offers a test of the two different models, and from the product (2) actually obtained, it is apparent that the frontier MO model is the one that provides the correct prediction.



7 8

While the frontier orbital model does correctly predict the regiochemistry of the dimer (2) formed from 1, it fails to anticipate the observed stereochemistry. Secondary orbital interactions should give rise to formation of the syn rather than the anti dimer, for maximum overlap of the lower and upper of the two singly occupied MO's in the excited molecule of 1 with, respectively, the HOMO and LUMO of the ground-state molecule, should favor a geometry leading to dimer with syn stereochemistry.[8] Presumably steric effects are responsible for formation of the anti dimer (2), and assuming that frontier orbital analysis provides the correct explanation of the dimer's regiochemistry, one concludes that secondary orbital interactions must be of lesser importance than such steric effects in the transition state for the photosensitized dimerization of 1.

Although the formation of 2 in this reaction was of theoretical interest for the reasons outlined above, the practical

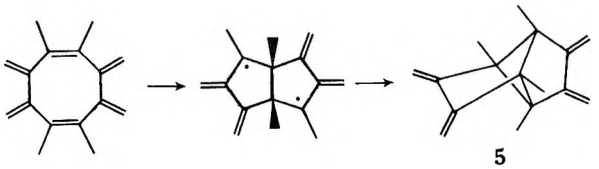
import of this result was that a convenient symthesis of **3** from **1** now seemed assured. Thermolysis of tricyclo[4.2.0.0^{2,5}]octane leads to 1,5-cyclooctadiene,[14] and by analogy there was little doubt that **2** would open to **3**. Indeed, on pyrolysis in a flow system at 240 °C the two required bonds were broken and **2** underwent smooth conversion to **3**. However, in contrast to the thermal reaction, direct photolysis of **2** led to cleavage of the two other allylic C–C bonds and the regeneration of **1**.[15]

The different courses taken by the thermal and photochemical reactions of **2** are readily understood. In the thermal reaction it is the most strained and, consequently, the weakest allylic C–C bonds in **2** that are cleaved. However, in the photochemical reaction the allylic bonds that are broken are those whose orientation causes them to mix strongly with π orbitals of the diene moieties. The analogous σ bonds in both isomers of tricyclo[4.2.0.0^{2,5}]octa-3,7-diene interact strongly with the π bonds, as revealed by the photoelectron spectra of these compounds.[16] The σ–π interaction is sufficiently large that the "through-bond" mediated mixing between the double bonds is stronger than that "through space," even in the syn isomer.[16] It is to be expected, therefore, that considerable σ–π mixing also exists in **2**. Specifically, the out-of-phase combination of localized bonding σ orbitals[17] mixes strongly with the symmetric (with respect to the C_2 axis present in **2**) combination of diene HOMO's, and the in-phase combination of antibonding σ orbitals mixes with the antisymmetric combination of the diene LUMO's. The MO's that result from the mixing are, respectively, the HOMO and the LUMO of **2**, each of which contains a substantial contribution from the appropriate combination of localized σ MO's. Although the excitation of an electron from the HOMO to the LUMO of **2** represents a forbidden electronic transition,[18] the resulting excited singlet state is the one of lowest energy.[19] Therefore, it is not unlikely that, following an allowed transition, **2** would undergo electronic relaxation to this singlet state. Population of this state is tantamount to excitation of an electron from an MO with appreciable bonding σ character to one with appreciable antibonding σ character. Not only are the two ring bonds in **2** thus weakened, but also, the excitation, if viewed in the extreme as involving predominantly these localized σ bonds, leaves populated just those orbitals required for a concerted and photochemically allowed $_{\sigma}2_s + {}_{\sigma}2_s$ retrograde cycloaddition.[20]

The photochemical cleavage of **2** to **1**, while of interest, especially as it contrasts with the thermal transformation of **2** to **3**, was certainly not synthetically useful and we did not investigate it further. Instead, we turned to the examination of the photochemistry of **3** in the hope that we could obtain **4** from **3** by direct irradiation. The desired closure is, of course, of the familiar butadiene → cyclobutene type, and precedent for the occurrence of this reaction in a molecule with some resemblance to **3** can be found in the photochemical transformation of 7,8-dimethylenecyclooctatriene to 1,2-ethanocyclooctatetraene.[22] On direct irradiation 1,2,5,6-tetramethylenecyclooctane also undergoes cyclobutene ring closure; however, transannular bond formation to give 2,6-dimethylene[3.3.2]propellane is competitive.[2] Transannular bond formation in **3**, particularly upon sensitization, which suppresses cyclobutene ring closure in tetramethylenecyclooctane,[2] therefore also seemed a likely photochemical event. Finally, photoinduced reaction of **3** at its internal double bonds too had precedent, not only in the photochemistry of 1,5-cyclooctadiene itself,[23] but also in that of 1,2:5,6-dibenzocyclooctatetraenes[24] and halogenated derivatives of dimethylenecyclooctatriene.[22]

When the irradiation of **3**, either direct or sensitized, was actually carried out, the last of these pathways was the one followed. The only isolable product showed three ^{1}H NMR signals at ($CDCl_3$) δ 0.70, 4.83, and 5.48 in the ratio 3:1:1, thus

Scheme II

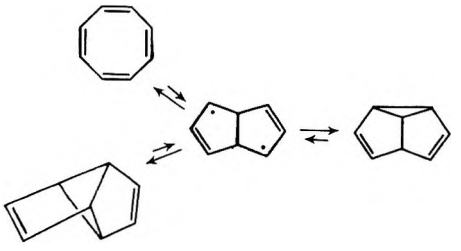


3 5

indicating that the molecule possessed four equivalent methyl and four equivalent methylene groups. The chemical shift of the methyl groups indicated that they were attached to saturated carbons, leading to the conclusion that the photoproduct was tricyclic. Thus, **5** and the syn isomer of **2** both provided reasonable structural assignments for the photoproduct. However, photochemical analogy[23,24] favored the former assignment, as did the occurrence of the methyl resonances in the photoproduct 0.35 ppm farther upfield than those in **2**, since magnetic shielding of equatorial methyl groups on puckered cyclobutane rings is a commonly observed phenomenon.[25] Further consideration of the syn isomer of **2** as the photoproduct was terminated by the discovery that, upon pyrolysis in a flow system at 380 °C or higher with a contact time of about 3 s, both **2** and **3** were converted to a single compound with the same ^{1}H NMR spectrum as the photoproduct.

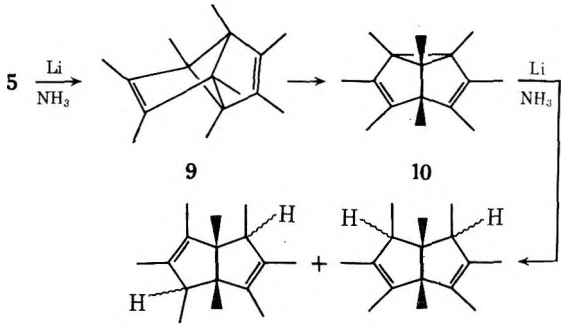
Although the finding that the photoproduct was also formed by pyrolysis of **3** eliminated on thermodynamic grounds the syn isomer of **2** as the molecule obtained from these reactions, the formation of **5** from **3** in the thermal rearrangement was, to say the least, surprising. The rearrangement of **3** to **5**, both photochemically and thermally, can be most easily rationalized, at least in a formal sense, in terms of the intermediacy of a biradical, as shown in Scheme II. A similar biradical intermediate has been suggested in the photochemical interconversion of cyclooctatetraene and semibullvalene[26] and in the thermal equilibration of substituted derivatives of these molecules.[27-29] The same biradical has also been postulated in the extraordinarily facile thermal transformation of bicyclo[3.3.0.0^{2,6}]octa-3,7-diene to semibullvalene.[30,31] These transformations are shown in Scheme III. The biradicals in the two schemes differ in that the double bonds that stabilize the biradical in Scheme III are endocyclic, so the formal shift of a double bond, necessary for the conversion of cyclooctatetraene and tricyclo[3.3.0.0^{2,6}]octa-3,7-diene into semibullvalene, can occur. In contrast, in the diradical in Scheme II the stabilizing double bonds are exocyclic and so, unlike the case in Scheme III, the exit to a semibullvalene derivative is blocked. A system similar to that portrayed in Scheme II has been investigated by Stiles and Burckhardt,[24] who explained the thermal and photochemical rearrangements of 1,2:5,6-dibenzocyclooctatetraenes by the intermediacy of tricyclic isomers analogous to **5**. However, Stiles and Burckhardt did not actually isolate the tricyclic isomers, a fact which is perhaps not surprising in view of the instability of tricyclo[3.3.0.0^{2,6}]octa-3,7-diene itself.[30] Thus, it seemed very strange, indeed, that we obtained **5** from pyrolysis of **3** at temperatures well above that at which tricyclo[3.3.0.0^{2,6}]-octane undergoes *cleavage* to 1,5-cyclooctadiene.[32] This,

Scheme III



however, was only the first of several apparently anomalous aspects of the chemistry of **5** that we encountered.[5]

The rearrangement of tricyclo[3.3.0.0^{2,6}]octa-3,7-diene to semibullvalene suggested a chemical method for proving the structure of **5**. Conversion of the exocyclic methylene groups of **5** into endocyclic double bonds should trigger rearrangement to a derivative of semibullvalene. Therefore, we investigated the reduction of **5**. Hydrogenation of **5** over a Pd/C catalyst, unlike the case in the reduction of **2**, proceeded 1,2 instead of 1,4. Consequently, **5** was reduced using lithium in a mixture of tetrahydrofuran, ammonia, and *tert*-butyl alcohol at −30 °C. The material isolated was not, however, octamethylsemibullvalene (**10**) but a mixture of octamethylbicyclo[3.3.0]octadienes, apparently resulting from a further two-electron reduction of **10**. This result might have been anticipated, since Schröder has reported the analogous reduction of bullvalene under similar conditions.[21] Indeed, when octamethylsemibullvalene (**10**) was itself subjected to the conditions of the reaction, the crude product mixture showed the identical ^{1}H NMR spectrum and GLC trace as the mixture of products obtained from reduction of **5**. It seems plausible, therefore, that under the reaction conditions **5** is, in fact, reduced to octamethyltricyclo[3.3.0.0^{2,6}]octa-3,7-diene (**9**), which rearranges to **10**, and that **10** then undergoes a further two-electron reduction to give the observed products. If this is actually the course taken by the reaction,[33] it indicates that **9** rearranges at a somewhat lower temperature (−30 °C) than the parent tricyclo[3.3.0.0^{2,6}]octa-3,7-diene, which apparently can be distilled at 0 °C.[30]



Another obvious method for converting the exocyclic methylenes of **5** into endocyclic double bonds is a Diels–Alder cycloaddition reaction. Besides providing further chemical proof of the structure of **5**, such a reaction labels the positions of the endocyclic double bonds present in the tricyclooctadiene that is expected to be formed initially. This labeling allowed a test of a proposed explanation for the rapid rearrangement of tricyclo[3.3.0.0^{2,6}]octa-3,7-dienes, involving a symmetry-allowed $_\sigma2_s + _\sigma2_a$ pathway from them to semibullvalenes.[34] The results of our studies of the cycloaddition reactions of **5** and the conclusions drawn from them are contained in the accompanying paper.[5]

Experimental Section

1,2-Dimethyl-3,4-dimethylenecyclobutene (1).[35] To a 100-mL round bottom flask equipped with a magnetic stirrer and reflux condenser was added 17.9 g of 3,4-dichlorotetramethylcyclobutene[36] and 38 g of quinoline. The mixture was heated at 120 °C under nitrogen for 0.5 h until two layers separated. Upon cooling, the lower layer solidified. The upper layer was decanted, water was added to the lower layer, and the resulting solution was extracted with hexane. The hexane extracts and the upper layer were combined and distilled under aspirator pressure. A colorless liquid, boiling at 35–40 °C, was collected and amounted to 6.2 g (60% yield). its NMR spectrum ($CDCl_3$) showed: δ 1.85 (s, 6 H), 4.44 (s, 2 H), 4.53 (s, 2 H); UV (hexane) λ_{max} 245 nm (log ε 3.8). Exact mass calcd for C_8H_{10}: 106.0783. Found: 106.0800.

***anti*-1,2,5,6-Tetramethyl-3,4,7,8-tetramethylenetricyclo[4.-2.0.0^{2,5}]octane (2).** In 60 mL of benzene was dissolved 0.8 g of benzophenone, and the solution was degassed in a photolysis well by bubbling nitrogen slowly through it for 2 h. After addition of 2.0 g of **1**, degassing was continued for another 0.5 h. The solution was photolyzed through a Pyrex filter with a 450-W Hanovia high-pressure lamp for 4 h. Although monitoring the reaction by NMR showed some starting material was still present, longer irradiation led to loss of product and lower overall yields. Upon termination of the photolysis, the solvent was removed under reduced pressure and the residue chromatographed over 30 g of neutral alumina, using pentane to elute the column. The product was collected in the first 50–75 mL. Evaporation of the solvent gave 0.9 g of off-white cyrstalline material; NMR ($CDCl_3$) δ 1.05 (s, 12 H), 4.70 (s, 4 H), 5.27 (4 H); UV (hexane) λ_{max} 243 nm (log ε 4.1). If the product was not stored under nitrogen at −78 °C, it decomposed, apparently to a polymer.[37] Polymerization also occurred rapidly when the crystals were heated to about 100 °C, so a melting point could not be obtained. Exact mass calcd for $C_{16}H_{20}$: 212.1565. Found: 212.1558.

Reduction of 2 to *anti*-Octamethyltricyclo[4.2.0.0^{2,5}]octa-3,7-diene (6). (a) Catalytically. A solution of 93 mg of **2** in 3 mL of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over 14 mg of a 5% palladium on carbon catalyst. During the course of 0.75 h 2 mol equiv of hydrogen were taken up. Filtration and evaporation of the solvent left 90 mg of colorless crystalline material. The product, after purification by recrystallization from methanol and/or sublimation, had an NMR spectrum ($CDCl_3$) that consisted of two singlets of equal area at δ 0.91 and 1.56 (lit.[10c] δ 0.89 and 1.54). Material of the highest melting point was obtained by purifying the crude product by preparative GLC at 180 °C on a 0.375 in. × 10 ft column of 20% SE-30 on Chromosorb W. Only one major peak was observed with a retention time of 8.5 min at a flow rate of 180 mL/min. The crystals that were collected melted very sharply at 125 °C (lit.[10a] 127 °C).

(b) With Lithium. To a 250-mL flask, equipped with an actone–dry ice condenser and a magnetic stirrer, was added 100 mg of lithium pieces under a nitrogen atmosphere. The flask was cooled in an acetone–dry ice bath and 50 mL of ammonia was distilled through a KOH trap and condensed in the reaction flask. Then 25 mL of tetrahydrofuran (distilled from lithium aluminum hydride) and 10 mL of *tert*-butyl alcohol (distilled from sodium) were added by syringe. Finally, 55 mg of **2** in 2 mL of tetrahydrofuran was added by syringe to the refluxing, stirred, blue solution. After 2 h the cold bath was removed and after another 0.5 h the reaction was quenched by adding a saturated aqueous solution of ammonium chloride until the blue color was discharged. Water and ether were added to the flask, which was allowed to stand at room temperature and then at 60 °C for 1 h to complete the removal of the ammonia. Further ether was added, the two layers were separated, the aqueous phase was extracted with more ether, and the organic layers were combined, washed with water and brine, and dried over magnesium sulfate. Removal of the solvent on a rotary evaporator left an oily solid, which was recrystallized from methanol and sublimed at 5 × 10^{-3} Torr at a bath temperature of 75 °C. The NMR spectrum of this material was identical with that prepared by catalytic reduction of **2**.

Photolysis of 2. (a) Direct. To a quartz NMR tube was added a solution of 20 mg of **2** in 0.5 mL of cyclohexane. The solution was degassed for 0.75 h by bubbling nitrogen slowly through it via a syringe needle that penetrated the septum with which the tube was capped. A shorter needle provided an outlet for the nitrogen. The needles were withdrawn and the NMR tube was irradiated with a 450-W Hanovia high-pressure lamp. After 1.5 h an NMR spectrum of the contents of the tube showed roughly 50% reversion of **2** to 1,2-dimethyl-3,4-dimethylenecyclobutene (**1**).

(b) Sensitized. To a Pyrex NMR tube was added a solution of 50 mg of **2** and 5 mg of benzophenone in 0.75 mL of benzene. After degassing, as described above, the tube was irradiated through a Pyrex filter with a 450-W Hanovia high-pressure lamp. A steady decrease in the concentration of **2** was observed by NMR with an attendant increase of a broad unresolved absorption in the aliphatic region. No trace of **1** was detectable. The disappearance of **2** was nearly complete after 1.5 h of irradiation.

Pyrolysis of 2. (a) At 240 °C to 1,2,5,6-Tetramethyl-3,4,7,8-tetramethylenecycloocta-1,5-diene (3). Using the flow system apparatus described previously,[2] 50 mg of **2**, dissolved in 0.5 mL of hexane, was added dropwise to the pyrolysis column, which was preheated to 240 °C. The nitrogen flow rate through the column was adjusted so that the residence time of the pyrolysate in the column was about 3 s. After the addition was complete, the column was washed with an additional 1.5 mL of hexane. The hexane solution was removed from the trap and evaporated. The NMR spectrum ($CDCl_3$) of the residue showed it to be pure **3**; δ 1.80 (s, 12 H), 4.80 (d, 4 H, J = 1.5 Hz), 5.10 (d, 4 H, J = 1.5 Hz).

(b) At 380 °C to 1,2,5,6-Tetramethyl-3,4,7,8-tetramethylenetricyclo[3.3.0.0^{2,6}]octane (5). A sample of **2** was pyrolyzed as described above, except that the temperature of the column was 380 °C. The NMR spectrum of the residue after solvent evaporation showed, in addition to a small amount of unresolved absorption in the aliphatic region, δ 0.70 (s, 12 H), 4.83 (s, 4 H), 5.48 (s, 4 H).

(c) At 300 °C to a Mixture of 3 and 5. A sample of **2** was pyrolyzed at 300 °C as described above. The NMR of the crude pyrolysate showed it to consist of an approximately 1:1 mixture of **3** and **5**. The products were separated by preparative GLC on a 0.375 in. × 10 ft column of 20% Carbowax 20 M on Chromosorb W. At 170 °C and a flow rate of 180 mL/min two peaks appeared with retention times of 10 and 17 min. These were collected and their NMR spectra were recorded. From the spectra the crystalline material with the shorter retention time was identified as **5** and the oily compound with the longer retention time as **3**. (Compound **5** appeared to polymerize at about 100 °C, so a melting point could not be determined). The UV spectrum (hexane) of **3** showed a single broad absorption with λ_{max} 240 nm (log ϵ 4.1), while that of **5** showed fine structure with λ_{max} 241 nm (log ϵ 4.0), 248 nm (log ϵ 4.1), and 259 nm (log ϵ 3.9). Exact masses calcd for $C_{16}H_{20}$: 212.1565. Found: 212.1586 for **3** and 212.1630 for **5**.

(d) By Injection into a GLC Instrument. Pure samples of **3** or **5** could be obtained by injection of **2** into a GLC instrument. At a column temperature of 160 °C **3** was the product collected. However, at 210 °C **5** was the principal product. The Carbowax column described above was used for preparing **3** in this way, while the SE-30 column was used for **5**.

Pyrolysis of 3 to 5. A sample of **3**, prepared by pyrolysis of **2** at 240 °C, was repyrolyzed in the flow system at 380 °C. The product was identified by NMR as **5**.

Photolysis of 3 to 5. (a) Direct. To a quartz NMR tube was added a solution of 20 μL of **3** in 0.5 mL of hexane. After degassing for 0.75 h, as described above, the solution was irradiated with a 450-W Hanovia high-pressure lamp for 0.5 h. Evaporation of the solvent left a slightly off-white crystalline solid, which was identified by NMR as **5**.

(b) Sensitized. To a Pyrex NMR tube was added a solution of 20 μL of **3** and 5 mg of benzophenone in 0.5 mL of benzene. After degassing for 1 h, the solution was irradiated through a Pyrex filter with a 450-W Hanovia high-pressure lamp. After 0.5 h the NMR spectrum showed clean and total conversion to **5**.

Reduction of 5 with Lithium in Ammonia–Tetrahydrofuran–*tert*-Butyl Alcohol. The reduction of 26 mg of **5** was carried out essentially as described above for **2**, except that the reaction was quenched by adding saturated ammonium chloride solution until the blue color was discharged before allowing the reaction mixture to warm. The product isolated was a colorless oil whose NMR spectrum ($CDCl_3$) showed a well resolved but complex series of sharp absorptions δ 0.8–1.2, a broad singlet with some fine structure δ 1.6, and a broad unresolved absorption δ 2.2–2.6. Integration gave the relative areas as 6:6:1. The mass spectrum of the product showed the molecular ion at M^+/e 218, confirming the addition of three moles of hydrogen. Analytical GLC on a 0.25 in. × 10 ft column of 5% Carbowax 20 M at 100 °C and a flow rate of 60 mL/min showed three peaks with retention times 10.5, 13.6, and 15.7 min and relative areas of approximately 1:2:1.

Reduction of Octamethylsemibullvalene (10). A 40-mg sample of **10**[27a] prepared by the literature procedure[38] was reduced under the same conditions as **5**. The NMR and the mass spectrum of the product and its GLC trace were all superimposable upon those obtained from the product of the reduction of **5**.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. Financial support was also provided by E. I. du Pont de Nemours & Co., the National Science Foundation, the Eli Lilly Co., and the Alfred P. Sloan Foundation.

Registry No.—**1**, 25467-12-3; **2**, 34101-24-1; **3**, 33507-29-8; **5**, 34106-16-6; **6**, 20380-33-0; 3,4-dichlorotetramethylcyclobutene, 1194-30-5.

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(30) J. Meinwald, D. Schmidt. and H. Tsuruta, *J. Am. Chem. Soc.*, **91**, 5877 (1969); H. E. Zimmerman, J. D. Robbins, and J. Schantl, *ibid.*, **91**, 5878 (1969). Alternatively, the reaction can be described as a forbidden $_{\pi}2_s + {}_{\sigma}2_s$ process.
(31) On irradiation, tricyclo[3.3.0.0^{2,6}]octadiene gives a mixture of semibullvalene and cyclooctatetraene; J. Meinwald and H. Tsuruta, *J. Am. Chem. Soc.*, **92**, 2579 (1970). Although the former product could originate from the same biradical, a concerted, photochemically allowed, 1,3 sigmatropic shift would also account for the formation of semibullvalene. A similarly allowed reaction of the $_{\pi}2_s + {}_{\sigma}2_s + {}_{\pi}2_s + {}_{\sigma}2_s$ type rationalizes the formation of the latter product.
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(33) Perhaps less likely, but nevertheless possible, is that the octamethyltricyclooctadiene (**9**) undergoes reduction with concomitant cleavage of the cyclobutane ring, so that rearrangement of **9** to octamethylsemibullvalene **10** is not involved.
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Cycloaddition Reactions of 1,2,5,6-Tetramethyl-3,4,7,8-tetramethylenetricyclo[3.3.0.0^{2,6}]octane. Evidence for Chemical Consequences of Orbital Interactions in Molecules Containing Unsaturatively 1,3-Bridged Cyclobutane Rings

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Received May 20, 1977

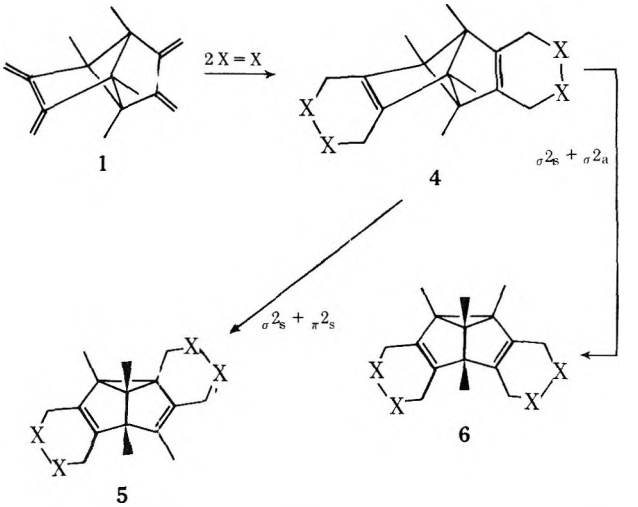
The title compound (1) reacts with tetracyanoethylene and *N*-phenyltriazolinedione to give rearranged adducts. Bond reorganization occurs after the first cycloaddition, and the structures of the products rule out a $_{\sigma}2_s + {}_{\sigma}2_a$ mechanism for rearrangement. With the latter dienophile an unrearranged monoadduct (**7b**) has been observed by NMR at low temperatures, and the activation parameters for its rearrangement to **8b** have been obtained. The energy of activation is consistent with that expected for a forbidden $_{\sigma}2_s + {}_{\pi}2_s$ process. The instability of molecules containing cyclobutane rings 1,3-bridged by ethylene, the contrasting thermal stability of **1**, and the reluctance of **1** to undergo Diels–Alder cycloaddition reactions are all rationalized by analysis of the interactions between the σ orbitals of the cyclobutane ring and the π orbitals of the unsaturated bridging groups. Calculations are reported that support this interpretation of the experimental results.

In the accompanying paper[2] we reported the transformation of 1,2,5,6-tetramethyl-3,4,7,8-tetramethylenetricycloocta-1,5-diene into 1,2,5,6-tetramethyl-3,4,7,8-tetramethylenetricyclo[3.3.0.0^{2,6}]octane (**1**), either by direct or sensitized photolysis or by pyrolysis. That **1** is formed in the thermal reaction is really most surprising, since tricyclo[3.3.0.0^{2,6}]octa-3,7-diene (**2**) is a very unstable compound, undergoing rapid rearrangement to semibullvalene (**3**) at room temperature.[3] Indeed, the thermal rearrangement of **2** to **3** is so facile for a reaction that either involves a diradical intermediate[3] or proceeds by a forbidden but concerted $_{\sigma}2_s + {}_{\pi}2_s$ mechanism[4] that a novel, symmetry allowed, $_{\sigma}2_s + {}_{\sigma}2_a$ pathway was proposed for this transformation.[5]

The availability of **1** appeared to afford an excellent opportunity to test whether a $_{\sigma}2_s + {}_{\sigma}2_a$ pathway was, in fact, involved in the rearrangement of **2** to **3**. Diels–Alder cycloadditions of 2 mol of a dienophile to **1** would provide **4**, a derivative of **2** in which the positions of the double bonds are labeled by the six-membered rings. Rearrangement of **4** by a forbidden $_{\sigma}2_s + {}_{\pi}2_s$ pathway, whether concerted or involving a diradical as a discrete intermediate, requires the formal shift of a double bond and leads to **5**. In contrast, since the π bonds are not involved in the $_{\sigma}2_s + {}_{\sigma}2_a$ mechanism, the labeling of the double bonds is different in the semibullvalene (**6**) that is the expected product if this pathway is utilized. Therefore, we undertook an investigation of the cycloaddition reactions of **1** in order to determine whether the semibullvalene formed had structure **5** or **6**.[6]

Results

To our surprise, compound **1** proved to be a most unreactive diene. Using such dienophiles as dimethyl acetylenedicarboxylate, dicyanoacetylene, and diethyl azodicarboxylate, we were unable to obtain an adduct of **1**. Although **1** did react with tetracyanoethylene (TCNE) to give a bis adduct, even with this potent dienophile reaction was surprisingly slow, requiring 2.5 h in refluxing tetrahydrofuran for completion. For comparison, the reaction of TCNE with 1,2-dimethylenecyclobutane in THF is instantaneous at room temperature.



The ^{1}H NMR spectrum of the TCNE bis adduct of **1** was entirely consistent with the formulation of its structure as **5** (X = C(CN)$_2$). Since **5** and **6** are both semibullvalenes, it was to be expected that both molecules would be rapidly fluxional at all but very low temperatures.[7] Whereas Cope rearrangement of **6** is not a degenerate process, the corresponding rearrangement of **5** is. Thus, on the NMR time scale **5**, because of its fluxionality, acquires an effective C_2 axis of symmetry, while **6** maintains only the plane of symmetry present in either of the nonequivalent divinylcyclopropane structures that can be written for it. Compounds **5** and **6** can, therefore, be most easily differentiated by the fact that the former should show only two types of methyl groups in its NMR spectrum, while the latter would be expected to exhibit three. At 100 MHz in acetone-d_6 the ^{1}H NMR spectrum of the TCNE bis adduct of **1** showed only two methyl resonances, thus leading to the assignment of its structure as **5**.[2b]

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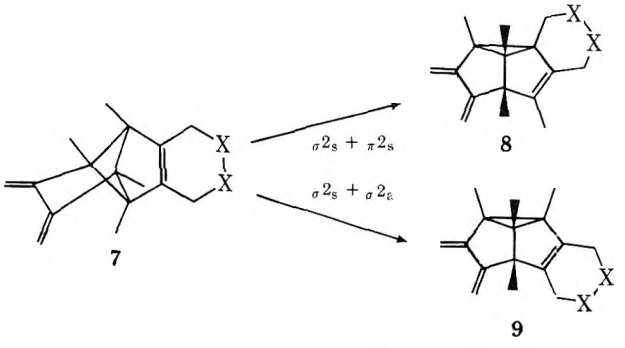
The observation of only two types of methyl resonances, although a necessary condition for assigning structure **5** to the bis adduct, is not sufficient to exclude conclusively structure **6**, for there exists the possibility that the two unique methyl groups in this latter structure might accidentally have the same chemical shift. If this were the case in one solvent, it might be that in another the accidental degeneracy would be lifted. It is also possible that the two methyl groups in one or more solvents might have slightly different chemical shifts but that higher magnetic fields are necessary to resolve them. Therefore, we obtained 220-MHz spectra of the TCNE bis adduct of **1** in both acetone-d_6 and pyridine-d_5,[8] but the two methyl resonances both remained sharp singlets. Although this finding increased our confidence that **5** did, in fact, represent the structure of the bis adduct, the possibility that we had obtained **6** instead could not be eliminated. Indeed, while additional NMR experiments could further increase the likelihood that **5** was the compound in hand, such studies could not unequivocally rule out **6**.

At this point we carried out an experiment which indicated that **4** was not involved at all in the transformation of **1** into the TCNE bis adduct that we had isolated. When the cycloaddition reaction between **1** and TCNE was conducted using only one equivalent of the dienophile, no monoadduct was isolated. Instead, a 1:1 mixture of the bis adduct and unreacted **1** was obtained. Clearly, the second Diels–Alder reaction must have been faster than the first. However, it was hard to see why cycloaddition at one diene unit of **1** to give **7a** should enhance the reactivity of the remaining diene moiety. On the other hand, the results of the experiment with one equivalent of TCNE could be rationalized if, under the reaction conditions, it was the monoadduct (**7a**) that rearranged. The chemistry of **1** indicated that the diene groups in it were unusually unreactive toward Diels–Alder cycloadditions, but there was no reason to believe that the diene units in either of the two possible rearrangement products, **8a** and **9a**, would exhibit anything but the high reactivity toward TCNE, usually observed in *cisoid* dienes. Thus, the initial slow cycloaddition to **1**, if followed by a rapid rearrangement of **7a** to **8a** or **9a**, would be expected to lead to reaction with a second molecule of TCNE at a rate much greater than the first.

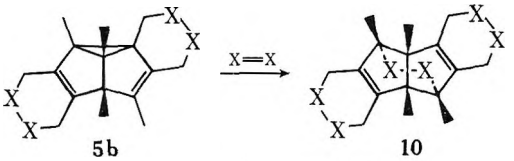


a, X = $C(CN)_2$; b, X—X = $\overline{NCON(Ph)CON}$

The interpretation of the experiment with one equivalent of TCNE in terms of the monoadduct (**7a**) as the species that rearranged suggested an interesting possibility for unequivocally resolving the question of the mechanism of the rearrangement. Unlike the diadducts, **5** and **6**, the monoadducts, **8** and **9**, can be unambiguously differentiated by NMR spectroscopy, since prior to the second cycloaddition these molecules lack the other endocyclic double bond that is required for fluxionality. Therefore, in the product (**8**) expected from the $\sigma 2_s + \pi 2_s$, or the equivalent diradical pathway, the formal shift required of the double bond in **7** would be signalled by the appearance in the NMR spectrum of a methyl group attached to a doubly bonded carbon. In contrast, since in the $\sigma 2_s + \sigma 2_a$ mechanism the double bonds are not involved, all the methyl groups remain attached to saturated carbon atoms in the product (**9**) expected from this pathway. Thus, we sought a dienophile that would allow us to isolate the rearranged monoadduct of **1**.

Such a dienophile was found in *N*-phenyltriazolinedione (PTAD). At 0 °C in $CHCl_3$ equimolar amounts of **1** and PTAD reacted to give a rearranged monoadduct to which the structure **8b** could unequivocally be assigned. In particular, a methyl group appeared at δ 1.51 in the ^1H NMR spectrum of this compound. Not only was the chemical shift about that expected for allylic methyl protons, but the resonance appeared as a doublet with J = 2 Hz. The proton to which it was coupled was centered at δ 3.70 and represented the upfield half of an AB quartet, J = 14 Hz, each of the two upfield components of which were further split into quartets, J = 2 Hz. The 2-Hz splittings are due to coupling between the methyl group and the allylic proton that lies in the π cloud of the adjacent double bond and which is consequently shielded by it.[9] The formation of **8b** is wholly consistent with the $\sigma 2_s + \pi 2_s$, or equivalent diradical pathway, but conclusively excludes a $\sigma 2_s + \sigma 2_s$ mechanism.

Further confirmation of the structure of **8b** came from its reaction with another equivalent of PTAD to yield the bis adduct (**5b**). The ^1H NMR spectrum of **5b** showed, as expected, only two methyl resonances. Interestingly, when **1** was allowed to react with 2 mol of PTAD at room temperature, the major product was not **5b** but a triadduct to which the structure **10** was assigned on the basis of the NMR spectrum. The formation of **10** had a parallel in the reaction of octamethylsemibullvalene with azoesters and TCNE,[10] and we did, indeed, find that octamethylsemibullvalene also reacted with PTAD.[11] In this case, however, not only was the diazalumibullvalene derivative corresponding to **10** isolated,[12] but the diazatriquinacene derivative was obtained as well. Although the former adduct might be the result of an allowed $\sigma 2_s + \pi 2_s + \pi 2_s$ cycloaddition, the presence of the latter compound and the facile equilibration of the two adducts in solvents of high dielectric constant led us to postulate a common dipolar intermediate in the formation of both the "allowed" and "forbidden" PTAD adducts.[11] More recently, Askani has found that PTAD adds to less alkylated semibullvalenes to give only the "forbidden" diazatriquinancene type products, and scrambling of the alkyl groups in the products again indicates the intervention of a dipolar intermediate.[13] Thus, it is likely that in the formation of the triadduct (**10**) a similar intermediate is involved, despite the fact that **10** could, in principle, result from a concerted cycloaddition.



X—X = $\overline{NCON(Ph)CON}$

The reason for the formation of the triadduct (**10**) when only 2 equiv of PTAD were used must be that either the cycloaddition to **1** or the rearrangement of **7b** is slow, compared to the cycloaddition to **8b** and the subsequent reaction of **5b** to give **10**. However, it was clear from the fact that the monoadduct (**8b**) could be isolated that the rearrangement must be the slow step. If the cycloaddition were the slow step, as it is in the reaction of TCNE with **1**, we would never have been able to obtain **8b**. It seemed possible, therefore, that we might be able to observe **7b** directly, before it rearranged to **8**. This did, in fact, turn out to be the case.

When 1 equiv of PTAD was added to a $CDCl_3$ solution of

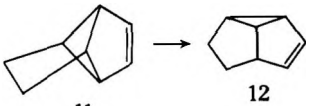
Table I. Rate Constants for the Rearrangement of 7b to 8b

T, °C	$k \times 10^3$, s^{-1}
16.2	0.259 ± 0.005
26.8	0.902 ± 0.030
34.4	2.36 ± 0.06
43.5	8.65 ± 0.40

1 in an NMR tube at −40 °C, no reaction occurred until the solution was warmed to −15 °C. At −5 °C the red color of the PTAD was completely discharged, and new singlets appeared in the ^{1}H NMR spectrum at δ 0.67 (6 H), 1.14 (6 H), 4.32 (4 H), 4.85 (2 H), and 5.48 (2 H).[14] The NMR spectrum of the unrearranged monoadduct (**7b**) remained unchanged for several hours at 0 °C; however, at higher temperatures transformation of **7b** to **8b** occurred. The rearrangement could be followed conveniently by NMR between 15 and 40 °C. The disappearance of **7b** could be monitored quantitatively by integration of the singlet at δ 0.67 and was found to follow good first-order kinetics. The rate constant for the rearrangement was obtained at four temperatures by least-squares fitting of the kinetic data. These rate constants and the probable errors in them are shown in Table I. As the temperature increased and the rearrangement became more rapid, the NMR method for following the reaction became less accurate, as indicated by the larger errors in the rate constants at the higher temperatures. A least-squares fit of the rate constants to the Arrhenius equation, $\log k = \log A - E_a/2.303RT$, gave $\log A = 13.9 \pm 1.1$ and $E_a = 23.2 \pm 1.2$ kcal/mol.

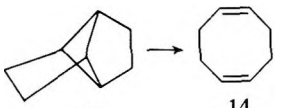
Discussion

Not only is the labeling study indicative of a $_\sigma 2_s + _\pi 2_s$ or equivalent diradical mechanism for the rearrangement of **7** to **8**, but the measured energy of activation is also in accord with such a pathway. Frey and Hopkins have found the activation energy for the rearrangement of tricyclo[3.3.0.0^{2,6}]-octene (**11**) to tricyclo[3.3.0.0^{2,8}]octene (**12**) to be 35.3 kcal/mol.[15] Neglecting all the possible effects on the rate that the four methyl[16] and two methylene[17] groups present in **7** might have, as well as the additional alkyl substitution on the endocyclic double bond, and focussing only on the additional stabilization of a putative diradical intermediate by one of the exocyclic double bonds, the energy of activation for the rearrangement of **7** should be lower than that for **11** by the allylic resonance energy.[18] The actual difference in activation energies of 12 kcal/mol is (probably fortuitously) close to the value of 12–13 kcal/mol for the allylic resonance energy, obtained by Doering and Beasley.[19]



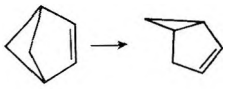
11 **12**

Because **7** is transformed rapidly to **8** at room temperature by a pathway that is forbidden in the Woodward–Hoffmann sense,[20] the rate of its rearrangement appears as a glaring anomaly. However, as pointed out above, the energy of activation for its rearrangement is lower than that for **11** by almost exactly the allylic resonance energy. Thus, the small magnitude of the activation energy for rearrangement of **11** is equally anomalous. Indeed, Frey has previously pointed out that the dramatic rate at which tricyclo[3.3.0.0^{2,6}]octadiene (**2**) rearranges to semibullvalene (**3**)[3] is consistent with an energy of activation for this process that is lower by only the allylic resonance energy than that for the transformation of **11** to **12**.[15] That the energy of activation for the rearrangement of **11** is, in fact, anomalously low can be judged by comparing it with that for the cleavage of tricyclo[3.3.0.0^{2,6}]octane (**13**) to 1,5-cyclooctadiene (**14**). If both reactions involve biradical intermediates, then, in the absence of other effects, the energy of activation for **11** → **12** should be approximately 12 kcal/mol lower than that for **13** → **14**. Since the energy of activation for the latter reaction is 56 kcal/mol,[21] the actual difference is 21 kcal/mol.

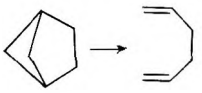


13 **14**

A similar disparity exists between the energy of activation for the rearrangement of bicyclo[2.1.1]hexene (**15**) to bicyclo[3.1.0]hexene and that for cleavage of bicyclo[2.1.1]hexane (**16**) to 1,5-hexadiene. Although the former process has been shown to proceed primarily by an allowed, concerted $_\sigma 2_a + _\pi 2_s$ pathway, the energetic advantage of the allowed over a forbidden or diradical pathway is known to be small.[15,22] Assuming, then, that the reactions again should vary in activation energy only by the allylic resonance energy, a difference of roughly 12 kcal/mol is expected. The observed energies of activation for the rearrangement of bicyclic compounds **15**[15] and **16**[23] are essentially the same as those for their tricyclic analogues, **11** and **13**. Thus, the activation energy for the rearrangement of the unsaturated compound is again on the order of 8–10 kcal/mol lower than expected.



15



16

Since an activation energy represents an energy difference, the anomalously low activation energies for rearrangement of molecules containing a cyclobutane ring 1,3-bridged by ethylene (e.g., **2**, **7**, **11**, and **15**) can be explained either by effects that lower the energy of the transition states or raise the energy of the reactants. Our labeling study, which rules out a $_\sigma 2_s + _\sigma 2_a$ mechanism for the rearrangement of one of these molecules (**7**), is consistent with a biradical (or a forbidden but concerted $_\sigma 2_s + _\pi 2_s$)[4] pathway, and the activation energy for the rearrangement of **7**, when compared with that for **11**, is also indicative of such a pathway. Therefore, there is little reason to believe that the anomalously low activation energies are the result of transition state stabilization. Thus, one is left with reactant destabilization as the probable cause of the rapid rearrangements. Such destabilization of molecules like **11** and **15**, relative to their saturated analogues, **13** and **16**, should be manifested in anomalously high heats of hydrogenation. Regrettably, to the best of our knowledge, no such measurements have been made to either **11** or **15**. Consequently, we must rely on the data from the kinetic studies to obtain an estimate of 8–10 kcal/mol as the apparent destabilization caused by the introduction of a double bond into **13** or **16** to give **11** or **15**.

Such an estimate is prone to error, for underlying it is the assumption that both the satuarted and unsaturated systems rearrange by transition states that may be described as biradical in nature, so that in the absence of differential reactant destabilization the unsaturated systems should have energies of activation that are lower by exactly the allylic resonance energy of 12 kcal/mol[19] than their saturated analogues. Even if this assumption is more or less valid, it is not at all certain that the actual magnitude of differential reactant destabilization will be manifested in the comparison of activation

energies since whatever effect operates to destabilize the reactant may, to some extent, still be present in the transition state for its rearrangement. Consequently, the estimate of 8–10 kcal/mol as the destabilization resulting from the removal of two hydrogen atoms from the saturated bridges in **13** and **16** could prove to be a lower limit.[24]

While the estimate of 8–10 kcal/mol as the destabilization energy in trading a saturated for an unsaturated cyclobutane bridging group may have to be revised when thermodynamic measurements on **11** and **15** become available, there is qualitative evidence, independent of the data from the kinetic studies discussed above, that such destabilization exists. For instance, the introduction of a double bond into **16** proved particularly difficult.[25] Enolate formation in bicyclo[2.1.1]-hexan-2-one is a factor of 10^4 slower at room temperature than in bicyclo[2.2.2]octan-2-one,[26] and enol formation is so difficult in the former ketone that it can be heated at 100 °C in neat HBr–Br_2 without undergoing bromination.[27]

What, then, is the cause of the destabilization that results from replacing an ethano with an etheno bridge? The internal bond angles at the trigonal carbons in both **11** and **15** are about 103°.[28] Clearly, the replacement of the tetrahedral carbons in **13** and **16** with trigonal centers must introduce additional angle strain. However, if this were the whole story, one would be hard pressed to explain why the tetramethylenetricyclooctane (**1**), which possesses four trigonal carbons, is apparently so stable, being *formed* from the corresponding tetramethylenecyclooctadiene at temperatures well above that at which tricyclo[3.3.0.$0^{2,6}$]octane (**13**) undergoes *cleavage* to cyclooctadiene (**14**).[2] The formation of **1** under these conditions points to the conclusion that, while introduction of ethylene as a 1,3 cyclobutane bridging group is destabilizing, in contrast, when a saturated bridge is replaced by butadiene, the result is a net stabilization. This conclusion is consistent with and supported by the lack of Diels–Alder reactivity of **1**, **7**, and related molecules[29] since in a Diels–Alder cycloaddition a butadiene is exchanged for an ethylene bridging group.

We have previously rationalized the apparent preference for butadiene over ethylene as a cyclobutane 1,3-bridging group in terms of interactions between the σ orbitals of the ring and the π orbitals of the bridging groups.[30] The cyclobutane ring possesses a degenerate pair of highest occupied MO's.[31] One of these HOMO's has the correct symmetry to interact with the filled π MO of a 1,3-bridging ethylene group. This interaction results in the existence of a very high-lying filled MO in molecules containing cyclobutane rings 1,3-bridged by ethylene, the presence of which is indicated by the long wavelength UV absorption of such molecules[30–32] and by their photoelectron spectra.[33] Chemically, the interaction between filled MO's has a net destabilizing effect, as revealed by calculations that include overlap.[30] Indeed, the orbital interaction between the HOMO's of the ring and bridge in a molecule like bicyclo[2.1.1]hexene (**15**) is reminiscent of that between the two ethylene units in cyclobutadiene, of which **15** may be considered a bis-homo derivative, and to which **15** has been compared.[34,35] In contrast to the case of ethylene, a butadiene bridging group has a lowest unoccupied MO (LUMO) that can mix with one of the HOMO's of the ring. This interaction is stabilizing,[30] and it is qualitatively similar to that between ethylene and butadiene in dimethylenecyclobutene, with which 2,3-dimethylenebicyclo[2.1.1]hexane (**17**) has been compared.[34] To continue the analogy, just as dimethylenecyclobutene does not undergo Diels–Alder reactions,[36] which would result in the replacement of butadiene by ethylene, so Diels–Alder reactions in molecules containing cyclobutane rings 1,3-bridged by butadiene (e.g., **1** and **7**)[29] are expected to be difficult.[37]

In previous studies[30,34] we have semiquantitatively estimated the destabilization that results from replacing a butadiene bridge with ethylene by calculating, using the extended Hückel (EH) method,[38] the heats of isodesmic reactions of the type shown in eq 1.

$$\mathbf{17} + \text{ethylene} \rightarrow \mathbf{15} + \textit{cisoid}\text{-butadiene} \quad (1)$$

The same technique can be used to investigate theoretically the consequences of replacing the saturated bridge in bicyclo[2.1.1]hexane (**16**) with the unsaturated one in bicyclo[2.1.1]hexene (**15**). We find the homodesmotic reaction[39] (eq 2)

$$\mathbf{16} + \textit{cis}\text{-2-butene} \rightarrow \mathbf{15} + \textit{cisoid}\text{-butane} \quad (2)$$

to be endothermic by 20 kcal/mol,[38,40] in agreement with the destabilization of **15**, relative to **16**, indicated by comparison of their energies of activation for rearrangement.

It is interesting to analyze why this reaction is unfavorable. As discussed above, angle strain must certainly contribute to destabilizing **15** relative to **16**, but there is also a contribution from orbital interactions. This is revealed by the π bond orders,[30] obtained from the EH calculations. As expected, the π bond orders, computed between the p orbitals perpendicular to the plane containing the four carbon atoms in *cisoid*-butane, are found to be nearly zero. In fact, they are found to be slightly negative, the calculated value being −0.012. The π bond orders between the ring and the saturated bridge in **16** are also found to be small and slightly negative, −0.007. Despite the use of a different geometry for **15**[40] than the one employed previously,[30] the π bond orders between ring and bridge are found to be almost the same, −0.009. Where does the destabilization in **15** come from then? Its source is revealed by comparison of the π bond orders in **15** with those in *cis*-2-butene. In the latter olefin the π bond orders between saturated and unsaturated carbons are positive and nearly 0.05 in magnitude. They reflect a stabilizing interaction between the π orbitals of the double bond and the pseudo π orbitals of the methyl groups.[42] In contrast, the π interaction between the ring and bridge in **15** is actually somewhat destabilizing.[43] Consequently, the double bond in **15** is abnormal in the sense that the π interaction between it and the two carbons attached to it causes a net destabilization of the molecule[43]—a marked difference between this double bond and the more typical one in 2-butene.

The energy calculated for the reaction in eq 3 should reflect the relative favorability of replacing the saturated bridge in **16** by butadiene, rather than by ethylene. Indeed, the computed endothermicity is reduced to only 2 kcal/mol.[38] The origin of the relative favorability of the reaction in eq 3, compared to that in eq 2, is again revealed by the EH π bond orders. While the calculated bond orders between the saturated and unsaturated carbons in 2,3-dimethylbutadiene are almost exactly the same as those in 2-butene, the π bond orders in **17** are, unlike those in **15**, positive. In fact, they are calculated to be 0.065,[44] which is larger in magnitude than those in 2,3-dimethylbutadiene. This result is in accord with the expectation that, with the proper unsaturated bridging group, a cyclobutane ring should be capable of a greater stabilizing conjugative interaction than methyl.[45] This fact explains why the reaction in eq 3 is calculated to be nearly thermoneutral[38] despite the increase in angle strain in going from **16** to **17**.

$$\mathbf{16} + \textit{cisoid}\text{-2,3-dimethylbutadiene} \rightarrow \mathbf{17} + \textit{cisoid}\text{-butane} \quad (3)$$

We have also used the calculated energies of homodesmotic reactions, similar to that in eq 1, to verify that in tricyclic systems like **1**, **2**, and **11**, where the cyclobutane ring is spanned by two unsaturated bridges, the net effect of the

bridging groups is additive. The reaction that replaces one ethylene in tricyclo[3.3.0.0^{2,6}]octadiene (2) by a butadiene bridge is found to be exothermic by virtually the same amount as the reaction that replaces the remaining ethylene by a second butadiene bridge, to give the hydrocarbon of which 1 is the tetramethyl derivative.[46] While this theoretical result confirms the expected additivity relationship,[24] the fact that these two numbers emerge from the EH calculations as almost *exactly* the same[46] and nearly identical with the energy now[40] calculated for the reverse of the reaction in eq 1 should probably be regarded as merely fortuitous.[47]

Conclusions

The labeling observed in and the activation parameters found for the thermal reorganization of 7 strongly indicate that this molecule and others (e.g., 2, 11, and 15) that contain cyclobutane rings 1,3-bridged by ethylene do not profit from any special stabilization of the transition states for their rearrangements. Instead, an ethylene bridge seems to exert a destabilizing effect in these molecules, resulting in their unusually low activation energies for rearrangement. This effect does not appear to be due entirely to angle strain since 1, a molecule possessing two unsaturated bridging groups, is formed at temperatures where the parent tricyclo[3.3.0.0^{2,6}]-octane fragments to 1,5-cyclooctadiene. Thus, it appears that, in contrast to the destabilizing effect of ethylene, the butadiene bridges in 1 exert a stabilizing influence. The postulates of destabilization by ethylene and stabilization by butadiene bridging groups are consistent with the lack of Diels–Alder reactivity observed in molecules containing cyclobutane rings bridged 1,3 by butadiene. These two effects are also manifested in the energies of homodesmotic reactions, computed by the EH method. The experimental and theoretical results discussed in this paper provide evidence of the importance, in molecules containing unsaturatively 1,3-bridged cyclobutane rings, of interactions between the σ MO's of the ring and the π MO's of the bridging groups.

Experimental Section

Reaction of 1,2,5,6-Tetramethyl-3,4,7,8-tetramethylenetricyclo[3.3.0.0^{2,6}]octane (1) with TCNE to Give 5a. A solution of 30 mg of 1 and 35 mg of tetracyanoethylene (TCNE) in 1 mL of freshly distilled tetrahydrofuran was placed in a 10-mL round bottom flask. Since permethylated semibullvalene derivatives are known to be sensitive to oxygen,[10] the solution was degassed by bubbling nitrogen slowly through it for 1.5 h. An aliquot showed no reaction between 1 and TCNE had occurred during this time. The solution was then refluxed for 2.5 h. Removal of the solvent under vacuum left a brown solid, whose NMR spectrum showed the formation of a single cycloadduct. Three recrystallizations from chloroform yielded shiny white crystals, mp 283–286 °C dec. The NMR spectrum at 100 MHz (acetone-d_6) showed δ 1.20 (s, 6 H), 1.80 (s, 6 H), 2.76 (d, 2 H, J = 17 Hz), 3.28 (s, 4 H), 3.88 (d, 2 H, J = 17 Hz). At 220 MHz[8] the broad singlet at δ 3.28 was resolved into an AB quartet, J = 17 Hz. Exact mass[50] calcd for $C_{28}H_{20}N_8$: 468.1811. Found: 468.1807.

Reaction of 1 with PTAD to Give Rearranged Monoadduct (8b). A solution of 59 mg of 1 in 0.5 mL of chloroform was placed in a vial containing a micro magnetic stirring bar and under an atmosphere of argon. The solution was cooled to 0 °C in an ice bath, and 49 mg (1 equiv) of *N*-phenyltriazolinedione (PTAD), prepared by the method of Stickler and Pirkle,[48] was added dropwise by syringe in 2 mL of chloroform. The solvent was removed under vacuum and the NMR spectrum of the residue indicated the formation of only one major product, which was purified by preparative TLC on alumina, using methylene chloride as solvent. In addition to material at the baseline, bands were observed at R_f 0.91 and 0.75. The band at R_f 0.75 yielded pure **8b** as a glass: NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.26 (s, 3 H), 1.42 (s, 3 H), 1.51 (d, 3 H, J = 2 Hz), 3.36 (d, 1 H, J = 12 Hz), 3.70 (d of q, 1 H, J = 14 and 2 Hz), 3.96 (d, 1 H, J = 12 Hz), 4.51 (s, 1 H), 4.62 (d, 1 H, J = 14 Hz), 5.02 (s, 1 H), 5.03 (s, 1 H), 5.39 (s, 1 H), 7.3–7.6 (m, 5 H). Exact mass calcd for $C_{24}H_{25}N_3O_2$: 387.1947. Found: 387.1950.

Reaction of 8b with PTAD to Give Diadduct (5b). The reaction of 20 mg of **8b** with 9 mg of PTAD in 3 mL of chloroform was carried out as described above for the preparation of **8b**. The product was again purified by preparative TLC on alumina, and a glassy solid was again obtained from the second band.[49] The NMR spectrum ($CDCl_3$) showed δ 1.11 (s, 6 H), 1.68 (s, 6 H), 3.70 (d, 2 H, J = 16 Hz), 4.02 (broad s, 4 H), 4.50 (d, 2 H, J = 16 Hz), 7.47 (s, 10 H). Exact mass calcd for $C_{32}H_{30}N_6O_4$: 562.2329. Found: 562.2320.

Reaction of 1 with 2 Equiv of PTAD at 25 °C to Give Triadduct (10). A solution of 12 mg of 1 in 3 mL of chloroform was added by syringe to a vial containing 20 mg of PTAD under a nitrogen atmosphere. After removal of the solvent under vacuum, the crude product was recrystallized from ethyl acetate to yield colorless crystals, mp 268–269 °C. The parent ion (M^+) at m/e 737 in the mass spectrum indicated a triadduct. The NMR spectrum ($CDCl_3$) showed δ 1.15 (s, 6 H), 1.94 (s, 6 H), 4.48 (broad s, 8 H), 7.40 (s, 5 H), 7.49 (s, 10 H). The three upfield signals appeared unusually broad. On cooling the NMR sample, further broadening was observed; on heating the sample, the lines sharpened.[12]

Reaction of 5b with PTAD to Give 10. A 5-mg sample of **5b** was dissolved in 0.5 mL of chloroform under argon and 17 mg of PTAD in 1 mL of chloroform was added at room temperature. After 1.5 h the solvent was removed under vacuum, and an NMR spectrum of the residue was obtained. It proved identical with that of **10**, obtained from the reaction of 1 with 2 equiv of PTAD.

Reaction of 1 with PTAD at −15 °C to Give Unrearranged Monoadduct (7b). A suspension of 10 mg (0.056 mmol) of PTAD in 0.5 mL of $CDCl_3$ was placed in an NMR tube and frozen at −78 °C. A solution of 15 mg (0.070 mmol) of 1 in 0.2 mL of $CDCl_3$ was added to the tube, which was placed in a variable temperature NMR probe at −40 °C. The probe was slowly warmed. At −15 °C a reaction was evident, which was completed by warming the tube to −5 °C. At this temperature the spectrum of **7b** was recorded: ($CDCl_3$) δ 0.67 (s, 6 H), 1.14 (s, 6 H), 4.32 (s, 4 H), 4.85 (s, 2 H), 5.48 (s, 2 H), 7.50 (s, 5 H).

Kinetics of the Rearrangement of 7b to 8b. A typical run was conducted by dissolving 10 mg of 1 in 0.2 mL of $CDCl_3$, adding the solution to an NMR tube, and cooling the tube to −78 °C. Then 9 mg of PTAD (slightly less than 1 equiv was always used) was added to the tube with a spatula and washed down the sides with 0.5 mL of $CDCl_3$. The NMR tube was then immersed in an ice bath at 0 °C and agitated frequently for 1.5–2 h to ensure mixing of the reactants. An NMR spectrum, taken at 0 °C, after this period showed the formation of **7b** but no detectable rearrangement to **8b**. The kinetics were run on a Varian HA-100 NMR spectrometer, equipped with a variable temperature probe. Before the tube containing **7b** was inserted, the probe temperature was determined, using a methanol standard and interpolating the temperature from the Varian calibration table. The instrument was tuned on a sample from a previous kinetic run, and the actual sample of **7b** was then inserted into the probe. Data collection was begun 90 s after sample insertion. The disappearance of **7b** was followed by rapid integration of the singlet at δ 0.67. The observed integrals were fitted by a standard least-squares program to the equation $\ln I = \ln I_0 - kt$, where I was the observed integral at time t, I_0 was the magnitude of the first integral, taken 90 s after sample insertion, and k was the derived rate constant, reported in Table I.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. Financial support was also provided by E. I. du Pont de Nemours & Co., the National Science Foundation, the Eli Lilly Co., and the Alfred P. Sloan Foundation.

Registry No.—1, 34106-16-6; **5a**, 33372-31-5; **5b**, 64235-49-0; **7b**, 64235-50-3; **8b**, 64235-51-4; **10**, 64235-52-5; TCNE, 670-54-2; PTAD, 4233-33-4.

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(12) One reason why we carried out the reaction of PTAD with octamethylsemibullvalene was that the PTAD triadduct (**10**) had a temperature-dependent NMR spectrum, and we wished to investigate the origin of this phenomenon in a simpler system. Although the temperature dependence could be due to slow flipping of the urazole rings in both molecules,[11] there is precedent for slow methyl group rotation in related systems [G. A. Olah, V. J. S. Staral, and L. Paquette, *J. Am. Chem. Soc.*, **98,** 1267 (1976)].
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(17) Some of the stabilizing π interaction between the two exocyclic double bonds present in **7** is presumably lost in the transition state for its rearrangement, where one double bond functions to stabilize an adjacent radical. In addition, the mixing between the orbitals of the butadiene bridge and those of the cyclobutane ring in **7** (vide infra) is altered in the transition state.
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(40) The choice of geometries for these calculations presents a problem. Experimental geometries for many of the molecules are unavailable, and even when geometries have been published, some have subsequently been shown to be in error.[28b] In previous studies we selectively manipulated experimental geometries to obtain coordinates for molecules whose structures had not been determined or the accuracy of whose structure we doubted.[30,34] In the calculations reported here we used MINDO/3 method [R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, **97,** 1285 (1975)] to find minimum energy geometries. However, as noted previously, MINDO energies for some of these molecules are expected to be even less reliable than the energies from EH calculations, because of the well-known inability of calculations that neglect overlap to account for destabilization due to interaction of filled MO's.[30] Therefore, we were forced to rely on EH calculations for energies at MINDO/3 geometries—an incongruity whose potential for error we fully appreciate. However, since the EH method for the calculation of energies is at best semiquantitative anyway, this procedure for generating geometries recommended itself by virtue of its convenience and a certain measure of internal consistency. If quantitatively accurate values for the energies of the isodesmic reactions reported here were desired, complete geometry optimization[41] and energy calculation by a reliable ab initio method would be the procedure of choice. The cost/benefit ratio of such an undertaking has, however, dissuaded us from pursuing such a study.
(41) It should be noted that total overlap populations between atoms in strained polycyclic systems depend much more critically on the choice of geometry than do the π bond orders that we have used to analyze our computational results.[30,34] Therefore, interpretations, based on total overlap populations, of calculations that do not include geometry optimization [see, for instance, P. Th. van Duijnen, P. van der Ploeg, H. Hogeveen, and W. F. J. Hurdeman, *Tetrahedron Lett.*, 573 (1975)] should be viewed with some caution.
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(43) As noted previously,[30] the magnitude of the destabilization is underestimated by analysis of just nearest neighbor π interactions between ring and bridge. The 1,3-π bond orders in **15** are also negative and much larger in magnitude, −0.208. The reason is that the mixing of the next to highest occupied MO of the cyclobutane ring with the LUMO of the bridge, which mitigates the destabilizing HOMO–HOMO interaction between nearest neighbors, actually enhances the magnitude of 1,3 π antibonding, since the mixing involves orbitals that are antisymmetric to the plane bisecting the double bond. Although 1,3-π overlap in **15** is only about a quarter of that between atoms 1 and 2, nevertheless the 1,3-π interaction is calculated (from comparison of the π overlap populations) to be more than five times as destabilizing as that between nearest neighbors. For similar reasons the 1,3-π bond orders in *cis*-2-butene are also expected to be negative, as, in fact, they are found to be by an EH calculation. Nevertheless, their magnitude is computed to be only a quarter the size of the 1,3-π bond orders in **15.**
(44) A previous EH calculation[30] at a different geometry[40] found these bond orders to be 0.078.
(45) Ab initio calculations [W. Hehre, *J. Am. Chem. Soc.*, **94,** 6592 (1972)] on vinylcyclopropane, vinylcyclobutane, and propene confirm that the stabilizing interaction between the four-membered ring and a double bond is greater than that of methyl but less than that of the three-membered ring.
(46) Actually, one would expect the reaction that replaces one ethylene bridge in **2** with butadiene to be more exothermic than the reaction that replaces the second since, in the molecule bridged by one butadiene and one ethylene the orbitals of the cyclobutane ring are not as contrained by symmetry as they are in the molecules that have two identical bridging groups. The energies of the two isodesmic reactions are calculated as −22.6 and −22.5 kcal/mol, respectively,[47] but the difference of only 0.1 kcal/mol cannot be regarded as at all significant. It should be noted, however, that, experimentally, **1** is a more reactive diene than **7b.** In fact, in the temperature range 0–15 °C rearrangement of **7b** competes effectively with the addition of a second mole of PTAD to it.
(47) The energy of the reaction in eq 1 is now calculated as +24 kcal/mol, whereas previously it was found to be +17 kcal/mol.[30] At the MINDO/3 geometries[40] **15** and **17** are found to be on the order of 60 kcal/mol higher in energy than previously. However, the increase in energy is greater for **15** by about 10 kcal/mol, but this is partially offset by a greater decrease in the energy of butadiene than in that of ethylene. It is amusing to note that if eq 3 is subtracted from eq 2, so that a reaction analogous to **1** is obtained but with ethylene and butadiene replaced by *cis*-2-butene and 2,3-dimethylbutadiene, the calculated energy is 18 kcal/mol—much closer to that computed previously for eq 1. The difference of 6 kcal/mol in the calculated energy of eq 1, depending on whether ethylene and butadiene or their dimethyl derivatives are used as reference, stems from the fact that the reaction, *cisoid*-butadiene + *cis*-2-butene → *cisoid*-2,3-dimethylbutadiene + ethylene, is computed (erroneously) to be exothermic by 6 kcal/mol.[40] The 6 kcal/mol difference in eq 1, due solely to which alkene and diene are chosen as reference, is indicative of the quantitative significance that should be attached to the energies reported here.
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(49) The band nearest the baseline was found to contain triadduct (**10**). An NMR spectrum of the crude product mixture showed **5b** and **10** to be the only products formed.
(50) Repeated attempts to obtain a correct elemental analysis on **5a** always gave results that were too low in C, H, and N. Given the extreme reactivity of octamethylsemibullvalene toward oxygen,[10] a reasonable hypothesis is that **5a**, itself a peralkylated semibullvalene, underwent some oxidation prior to being analyzed.

Alkyl Nitrate Nitration of Active Methylene Compounds. Nitration of Aldimines[1]

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Received June 20, 1977

The alkyl nitrate nitration of aldimines **1** derived from aldehydes and aliphatic or alicyclic amines affords the corresponding 1-alkylamino-2-nitro-1-alkenes **2**. The spectral data of **2** show the presence of both the *Z* and *E* isomers, the former predominating in both the solid state and in nonpolar solvents.

In continuation[2] of our studies of the alkyl nitration, we are now reporting on its application to the synthesis of 1-alkylamino-2-nitro-1-alkenes **2** (eq 1).

$$\underset{\mathbf{1}}{RN{=}CHCH_2R'} \xrightarrow[2.\ NH_4Cl]{1.\ KNH_2\text{–liquid } NH_3\text{–}RONO_2} \underset{\mathbf{2}}{RNCH{=}CR'} \quad (1)$$
(H on N, NO_2 on C)

Methods that have been used to prepare **2** include the condensation of sodium nitromalonaldehyde with hydrochlorides of primary and secondary amines;[3] the condensation of α-nitro ketones with primary aromatic amines;[4] the reaction of morpholine and piperidine with alkoxyalkylidenemalonic esters and nitromethane;[5] the reaction between sodium methazonate and salts of primary[6a] and secondary amines;[6b] the reaction of vicinal dinitroalkenes[7a] or chloronitroalkenes[7b] with amines; and the condensation of nitroalkanes with N,N-disubstituted amide acetals[8] or with amide–dimethyl sulfate complexes.[9]

A consideration of the available methods has shown that they are limited in scope. Moreover, they suffer from the lack of readily available starting materials and frequently from low yields.

The nitration reaction in eq 1 was studied in several base–solvent systems with *N*-propylidene-*tert*-butylamine [**3**, R = $C(CH_3)_3$; R′ = CH_3] and *N*-butylidene-*tert*-butylamine [**4**, R = $C(CH_3)_3$; R′ = C_2H_5] as model compounds. As shown in Table I, the highest yields of 1-(*tert*-butylamino)-2-nitro-1-propene (**5**) and of 1-(*tert*-butylamino)-2-nitro-1-butene (**6**) (53 and 51%, respectively) were obtained in the potassium amide–liquid ammonia system when the molar ratio of **1** to base to nitrating agent was 1:2:1.5 and when 30 min was allowed for both anion formation and nitration. It is of interest that in a control test only 18% of **3** was recovered when it was subjected to potassium amide in liquid ammonia. A considerable amount of polymeric material was formed which was not identified. Only tar-like material was obtained when **3** was nitrated in lithium amide–liquid ammonia.

Nitration of **4** in *n*-butyllithium–hexane did not give **6** but, instead, afforded (*N*-*tert*-butyl)-4-aminooctane (**7**) which arose from a nucleophilic attack of butyllithium on the azomethine carbon[10] (eq 2). Nitrations of **4** with *n*-propyl nitrate were successful in lithium diisopropylamide employing hexane or THF as solvents, but the yield of **6** did not exceed 30%.

In order to determine the scope of the reaction, aldimines of varied structures were nitrated. Variations in the alkylamino moiety had some effect on the yield of the aminonitroalkenes **2** as indicated in Table II. The low yield of 1-(isopropylamino)-2-nitro-1-propene (**8**) is probably due to its instability. It decomposed on recrystallization from hot hexane with the evolution of oxides of nitrogen and also on standing at ambient temperatures.

$$\underset{\mathbf{4}}{(H_3C)_3CN{=}CH(CH_2)_2CH_3} \xrightarrow[2.\ H^+]{1.\ BuLi\text{–}C_6H_{14}\text{–}n\text{-}PrONO_2} \underset{\mathbf{7}}{H_3C(CH_2)_2CH(CH_2)_3CH_3} \quad (2)$$
(HNC(CH$_3$)$_3$ on the CH)

As shown in Table II, aldimines derived from primary aliphatic aldehydes underwent nitration in the potassium amide–liquid ammonia system to afford the expected aminonitroalkenes.

An interesting side reaction was observed in the nitration of *N*-ethylidene-*tert*-butylamine [**9**, R = $C(CH_3)_3$; R′ = H] with *N*-propyl nitrate. In addition to 1-(*tert*-butylamino)-2-nitroethene (**10**) there was also formed compound **5** in 10% yield (eq 3). Only **10** was obtained when **9** was nitrated with

$$\underset{\mathbf{9}}{(CH_3)_3CN{=}CHCH_3} \xrightarrow{1.\ KNH_2\text{–liquid } NH_3} \quad (3)$$
$$\xrightarrow[2.\ EtONO_2]{3.\ NH_4Cl} \underset{\mathbf{10}}{(CH_3)_3CNHCH{=}CHNO_2}$$
$$\xrightarrow[2.\ n\text{-}PrONO_2]{3.\ NH_4Cl} \underset{\mathbf{5}}{(CH_3)_3CNHCH{=}C(NO_2)CH_3} + \mathbf{10}$$

ethyl nitrate. Traces of **5** were also found in nitrations of **4** and *N*-heptylidene-*tert*-butylamine with *n*-propyl nitrate.

The formation of **5** in these reactions is very likely due to aldehyde interchange between the aldimines and propanal. In a control test it was established that **3** was formed in addition to considerable amounts of aldol condensation products when **4** was treated with propanal in potassium amide–liquid ammonia (eq 4).

$$\mathbf{4} + H_3CCH_2CHO \xrightarrow[2.\ NH_4Cl]{1.\ KNH_2\text{–liquid } NH_3} \underset{\mathbf{3}}{(H_3C)_3CN{=}CHCH_2CH_3} + \mathbf{4} \quad (4)$$

The formation of propanal in the nitrations with *n*-propyl

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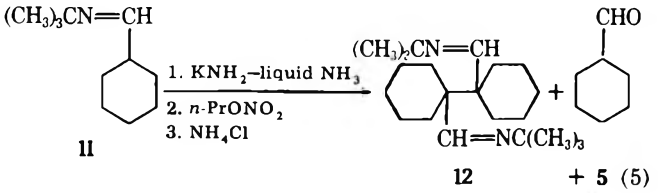
nitrate is not unexpected for it has been well established that primary alkyl nitrates undergo elimination reactions in alkaline media to give aldehydes.[11]

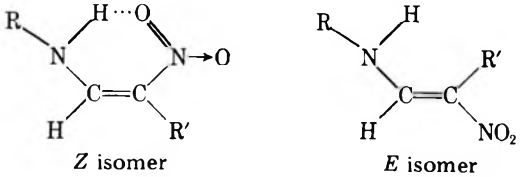
Alkyl nitrate nitrations of aldimines derived from α-branched aldehydes did not lead to *tert*-α-nitroaldimines. Instead, products were obtained which resulted both from dimerization of the aldimine and aldehyde interchange. For example, nitration of cyclohexylmethylidene-*tert*-butylamine (**11**) with *n*-propyl nitrate afforded 1,1′-bis(cyclohexylmethylidene-*tert*-butylamine) (**12**, 18%), cyclohexanecarboxaldehyde, and compound **5** (eq 5). The structure of **12** was



assigned on the basis of its NMR spectrum which showed singlets at 1.20 and 7.34 ppm for the *tert*-butyl and methine protons, respectively. The cyclohexyl rings were indicated by two types of ring protons, namely, a 16-proton multiplet at 1.80 ppm and a four-proton multiplet at 2.00 ppm. The latter is ascribed to the axial hydrogens in the 2 and 6 positions which are shielded by the imino groups.

Recently, we reported that alkyl nitrations of 2- and 4-isopropylpyridines led with dimerization to the 2,3-bis(pyridyl)-2,3-dimethylbutanes. It was shown that the nitroisopropylpyridines were intermediates in these transformations.[12] It is possible, although it has not been verified, that a tertiary nitro compound such as *N*-(1-nitrocyclohexylmethylidene)-*tert*-butylamine was the precursor in the formation of dimer **12**.

Spectra of Compounds 2. A study of the NMR spectra of compounds **2** clearly confirmed their structures as aminonitro olefins. In solution, both *E* and *Z* isomers were present. The *Z* isomer predominated in nonpolar solvents due to its increased stability through intramolecular hydrogen bonding. The *Z* and *E* isomers were distinguishable by the different chemical shifts of the olefinic protons. For example, in $CDCl_3$ they appeared in compound **5** as doublets at 7.09 and 8.41 ppm which integrated to a value of 0.9 and 0.1 protons, respectively. The *E* isomer absorbed at lower field because of the de-

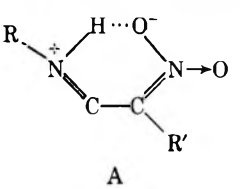


R = alkyl; R′ = H, alkyl

shielding effect of the *cis*-nitro group.[13] The resonances appeared as doublets due to vicinal HCNH coupling between the amino and olefinic protons. The existence of the coupling was demonstrated by deuterium exchange and spin-decoupling experiments. Irradiation of the NH absorption at 9.6 ppm caused the collapse of the olefinic proton resonances to singlets. Moreover the large coupling constant of 14 Hz is indicative of the trans conformation for the amino and olefinic protons.[14]

Addition of $(CD_3)_2SO$ to a $CDCl_3$ solution of **5** caused a change of the *Z*/*E* isomer ratio from 9:1 to 1:1. A similar solvent-promoted isomerization has also been observed with α-nitroarylidenephenylhydrazines.[15]

In the solid-state infrared spectra (KBr, CsI) of compounds **2**, the presence of the NH group was clearly apparent as a single, moderately intense absorption at 3200 cm^{-1}. In chloroform solution, this band was replaced by two weak absorptions at 3570–3330 cm^{-1} (concentration dependent) and at 3279–3225 cm^{-1} (concentration independent). These were assigned, respectively, to the free and associated (hydrogen bonded) forms of **2**. All of compounds **2** exhibited a sharp absorption at 1660–1630 cm^{-1}. This band, which is very likely due to the C=C vibration, possibly also reflects contribution from the C=N stretching vibrations of the dipolar structure A. Similar absorptions have been observed in the spectra of aminonitroacroleins[16] and aminonitroalkenes.[6a,17]



A

The conjugative effect of the alkylamino group was also seen in the shift to lower frequencies of the nitro group to 1371–1353 cm^{-1}. In nitroalkenes the asymmetric stretching vibration of the nitro group occurs at 1550–1500 cm^{-1}.[18]

The mass spectra of **2** exhibited molecular ions which corresponded to the appropriate molecular formulas. In compounds **2** which contained the *tert*-butylamino moiety, frag-

Table I. Effect of Various Base–Solvent Systems on the Yield of $(H_3C)_3CNHCH{=}C(NO_2)R$ (5, R = CH_3; 6, R = CH_2CH_3)

Base–solvent	5, yield, %	6, yield, %
KNH_2–liquid NH_3[a]	53	51
$NaNH_2$–liquid NH_3[a]	44	
$LiNH_2$–liquid NH_3[a]	0[b]	
n-BuLi–hexane[c]		0[d]
$(i\text{-Pr})_2$NLi–hexane[c,e]		30
$(i\text{-Pr})_2$NLi–THF[c,f]		28

[a] The molar ratio of 1 to base to *n*-propyl nitrate was kept at 1.0:2.0:1.5 in approximately 200 mL of solvent. Acidifications were carried out in situ with ammonium chloride. [b] Extensive tar formation was observed. [c] The molar ratio of 1 to base to *n*-propyl nitrate was 1:1:1.5. The reaction mixture was acidified with hydrogen chloride. [d] A 40% yield of (*N*-*tert*-butyl)-4-octanamine (**7**) was isolated. [e] When the molar ratio of base was increased to two, the yield of **6** was only 14%. [f] The reaction mixture was acidified in situ with glacial acetic acid.

Table II. Preparation of $RNHCH{=}C(NO_2)R'$[a,b]

R	R′	Yield, %	Mp, °C
$t\text{-}C_4H_9$	H	21[c,d]	81–82
$n\text{-}C_3H_7$	CH_3	54	*e*
$i\text{-}C_3H_7$	CH_3	40	62.5–63 dec
$i\text{-}C_4H_9$	CH_3	70	*e*
$t\text{-}C_4H_9$	CH_3	51	113–113.5
C_6H_{11}	CH_3	50	101–101.5
$t\text{-}C_4H_9$	C_2H_5	51[f]	91.5–92
$n\text{-}C_6H_{13}$	C_2H_5	67	*e*
$t\text{-}C_4H_9$	$n\text{-}C_5H_{11}$	46[f]	77.5–78

[a] Satisfactory analytical data were reported for all new aldimines and new alkylaminonitroalkenes. [b] Nitrations were performed in 150–200 mL of liquid ammonia at −33 °C, employing 0.10 mol of imine, 0.20 mol of potassium amide, and 0.15 mol of *n*-propyl nitrate. Anion formation and nitration times were 30 min. Acidification was performed in situ with 0.22 mol of ammonium chloride. [c] About 10% of 1-(*tert*-butylamino)-2-nitropropene (**5**) was also obtained as determined by NMR. [d] The yield was 13.8% when using ethyl nitrate. [e] Undistillable liquid. [f] Traces of **5** were present in the crude reaction mixture as determined by NMR.

mentation was dominated by the loss of methyl and isobutylene. Compounds **2** which did not contain the *tert*-butylamino group generally exhibited one or more ions which indicated the loss of the fragments OH, NO_2, or HNO_2. The frequent occurrence of the P − OH and P − HNO_2 ions suggests a molecular geometry in which the nitro group and a hydrogen atom are in close proximity, enabling the concerted loss of these fragments. This is consistent with the existence of **2** in the *Z* configuration.

Experimental Section

Apparatus. Nitrations were performed in a 300- or 500-mL four-necked flask equipped with a mechanical stirrer, dry ice condenser, thermometer, and pressure-equalizing addition funnel. The ammonia was passed through a potassium hydroxide tower prior to liquefaction.

***N*-Propylideneisobutylamine.** The following modification of the method of Campbell et al.[19] is representative of the procedure employed for the preparation of aldimines.

To 58.0 g (1.00 mol) of freshly distilled propanal at −20 °C was added dropwise, with stirring and cooling, 73.0 g (1.00 mol) of freshly distilled isobutylamine, while maintaining the temperature below −5 °C. Solid potassium hydroxide (~10 g) was added, and the reaction mixture was allowed to warm to room temperature while the aqueous layer separated (~1 h). The organic phase was stored over potassium hydroxide at 5 °C overnight and then distilled from fresh potassium hydroxide through a 40-cm Todd column packed with 0.25-in. glass helices to give *N*-propylisobutylamine (45.8 g, 40%): bp 115–116 °C; $n^{21}D$ 1.4092; IR ($CHCl_3$) 1669 cm^{-1} (C=N); NMR ($CDCl_3$) 0.89 [d, 6, $(CH_3)_2CH$], 1.08 (t, 3, CH_2CH_3), 1.4–2.5 [m, 3, CH_2CH_3 and $(CH_3)_2CH$], 3.19 (d, CH_2N), and 7.62 ppm (t, 1, CH=N).

***N*-Heptylidene-*tert*-butylamine (83%):** bp 51–52 °C (3 mm); $n^{21}D$ 1.4269; IR (neat) 1667 cm^{-1} (C=N); NMR ($CDCl_3$) 1.16 (m, 20, CH_2 and CH_3), 2.17 (m, 2, CH_2), and 7.60 ppm (t, 1, CH=N).

***N*-Butylidene-*n*-hexylamine (63%):** bp 107–110 °C (48 mm); $n^{20}D$ 1.4290; IR (neat) 1681 cm^{-1}; NMR ($CDCl_3$) 0.90 (t, 6, CH_3), 1.45 (m, 10, CH_2), 2.20 (m, 2, CH_2CH=N), 3.34 (t, 2, CH_2N), and 7.60 ppm (t, 1, CH=N).

***N*-Cyclohexylmethylidene-*tert*-butylamine (71%):** bp 54–54.4 °C (3 mm); $n^{20}D$ 1.4515; IR (neat) 1669 cm^{-1} (C=N); NMR ($CDCl_3$) 1.14 [s, 9, $(CH_3)_3C$], 1.2–2.2 (m, 11, CH_2 and CH, ring), and 7.42 ppm (d, 1, CH=N).

1-(*tert*-Butylamino)-2-nitro-1-propene (5). The following experiment is typical of the procedure employed in the nitration of aldimines.

To 150 mL of liquid ammonia at −33 °C was added a catalytic amount of ferric nitrate and freshly cut potassium metal (7.82 g, 0.20 g-atom). After the potassium amide had formed (15–30 min), freshly distilled *N*-propylidene-*tert*-butylamine[20] (11.3 g, 0.10 mol) was added in one portion. The reaction mixture was stirred at −33 °C for 0.5 h and then cooled to −60 °C, and *n*-propyl nitrate (15.8 g, 0.15 mol) was added during 5–8 min, while maintaining the temperature below −40 °C (*Caution:* cooling must be maintained during the addition of the nitrating agent, as long as the vigorous exotherm persists). The nitration mixture was stirred for an additional 25 min at −33 °C and then acidified at −40 °C with ammonium chloride (11.8 g, 0.22 mol).

The ammonia was replaced with absolute ether, the inorganic salts were filtered off, and the ether was removed in vacuo to give an orange oil. The oil was triturated with hexane, cooled to induce crystallization, and filtered. The orange amorphous solid (9.53 g, 60%) was dissolved in hexane, treated with decolorizing carbon, and recrystallized to afford 1-(*tert*-butylamino)-2-nitro-1-propene (**5**) (8.38 g, 53%): yellow needles; mp 113–113.5 °C; UV λ_{max} (95% C_2H_5OH) 370 nm (log ϵ 4.86) and 260 (3.11); IR ($CHCl_3$) 3236 (NH), 1645 (C=C or C=N), 1355, 1318, and 1239 cm^{-1} (NO_2); NMR ($CDCl_3$) 1.38 [s, 9, $(CH_3)_3C$], 2.06 (s, 3, CH_3), 7.09 (d, 0.9, C=CH, *Z* isomer, *J* = 14 Hz), 8.41 (d, 0.1, C=CH, *E* isomer, *J* = 14 Hz), and 9.6 ppm (br, 1 NH); mass spectrum (75 eV) *m/e* (rel intensity) 158 (42), 143 (38), 102 (22), 84 (17), 57 (100); mol wt (C_6H_6) calcd 158.2, found 162.0.

1-(*n*-Propylamino)-2-nitro-1-propene. From potassium (7.82 g, 0.20 g-atom), *N*-propylidene-*n*-propylamine[21] (9.90 g, 0.10 mol), *n*-propyl nitrate (15.8, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 200 mL of liquid ammonia, there was obtained 23.5 g of a dark brown liquid which did not crystallize.

A 5.00-g portion was chromatographed on a 13 × 2.5 cm silica gel column and eluted with ether to afford 1-(*n*-propylamino)-2-nitro-1-propene (1.70 g, 54%): nondistillable yellow liquid; $n^{22}D$ 1.5793; UV λ_{max} (95% C_2H_5OH) 370 nm (log ϵ 3.97) and 257 (2.90); IR ($CHCl_3$) 3279 (NH), 1660 (C=C or C=N), 1366, 1325, and 1239 cm^{-1} (NO_2); NMR ($CDCl_3$) 0.99 (t, 3, CH_3), 1.67 (m, 2, CH_2), 2.07 (s, 3, CH_3), 3.40 (m, 2, CH_2), 7.10 (d, 0.9, C=CH, *Z* isomer, *J* = 14 Hz), 8.36 (d, 0.1, C=CH, *E* isomer, *J* = 14 Hz), and 9.5 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 144 (31), 127 (1.1), 115 (19), 98 (1.1), 97 (9.0), 68 (23), 58 (72), 43 (100), 41 (98); mol wt [$(CH_3)_2CO$] calcd 144.17, found 143.16.

1-(Isopropylamino)-2-nitro-1-propene (8). From potassium (7.82 g, 0.20 g-atom), *N*-propylideneisopropylamine[22] (9.90 g, 0.10 mol), *n*-propyl nitrate (15.8 g, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 100 mL of liquid ammonia, there was obtained an amorphous red-orange solid (9.53 g, 66%). Recrystallization from hexane afforded 8 (5.73 g, 40%): yellow needles; mp 62.5–63 °C dec; UV λ_{max} (95% C_2H_5OH) 368 nm (log ϵ 4.21) and 262 (3.00); IR ($CHCl_3$) 3247 (NH), 1647 (C=C or C=N), 1360, 1299, and 1235 cm^{-1} (NO_2); NMR ($CDCl_3$) 1.28 [d, 6, $(CH_3)_2CH$], 2.00 (s, 3, CH_3), 3.67 [m, 1, $(CH_3)_2CH$], 7.08 (d, 0.9, C=CH, *Z* isomer, *J* = 14 Hz), 8.33 (d, 0.1, C=CH, *E* isomer, *J* = 14 Hz), and 9.4 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 144 (77), 129 (43), 111 (17), 97 (20), 85 (28), 82 (41), 58 (82), 56 (41), 55 (41), 43 (100).

1-(Isobutylamino)-2-nitro-1-propene. From potassium (7.82 g, 0.20 g-atom), *N*-propylideneisobutylamine (11.3 g, 0.10 mol), *n*-propyl nitrate (15.8 g, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 150 mL of liquid ammonia, there was obtained 24.1 g of a dark orange oil which did not crystallize. The oil was chromatographed on a 30 × 2.5 cm silica gel column and eluted with ether. The ether was removed in vacuo and the product was rechromatographed to afford 1-(isobutylamino)-2-nitro-1-propene (10.5 g, 70%): yellow-brown liquid; $n^{21}D$ 1.5832; UV λ_{max} (95% C_2H_5OH) 369 nm (log ϵ 3.98) and 243 (3.15); IR ($CHCl_3$) 3270 (NH), 1658 (C=C or C=N), 1371, 1323, and 1239 cm^{-1} (NO_2); NMR ($CDCl_3$) 0.95 [d, 6, $(CH_3)_2CH$], 1.0 [m, 1, $(CH_3)_2CH$], 2.05 (s, 3, CH_3), 3.27 (t, 2, CH_2N), 7.08 (d, 0.9, C=CH, *Z* isomer, *J* = 14 Hz), 8.28 (d, 0.1, C=CH, *E* isomer, *J* = 14 Hz), and 9.5 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 158 (39), 142 (2), 125 (4), 115 (65), 111 (10), 69 (36), 58 (100).

1-Cyclohexylamino-2-nitro-1-propene. From potassium (13.1 g, 0.34 g-atom), *N*-propylidenecyclohexylamine[23] (23.3 g, 0.17 mol), *n*-propyl nitrate (35.1 g, 0.33 mol), and ammonium chloride (19.8 g, 0.36 mol), in 150 mL of liquid ammonia, there was obtained an amorphous yellow-orange solid (18.3 g, 60%). Recrystallization from hexane gave 1-cyclohexylamino-2-nitro-1-propene: 15.7 g (50%); lustrous yellow plates; mp 101–101.5 °C; UV λ_{max} (95% C_2H_5OH) 370 nm (log ϵ 4.09) and 258 (2.86); IR ($CHCl_3$) 3225 (NH), 1652 (C=C or C=N), 1364, and 1299 cm^{-1} (NO_2); NMR ($CDCl_3$) 1.0–2.0 (m, 10, CH_2, ring), 2.04 (s, 3, CH_3), 3.0–3.6 (br, 1, CH, ring), 7.03 (d, 0.9, C=CH, *Z* isomer, *J* = 14 Hz), 8.32 (d, 0.1, C=CH, *E* isomer, *J* = 14 Hz), and 9.5 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 184 (76), 167 (10), 149 (20), 141 (26), 138 (19), 121 (metastable), 109 (18), 103 (22), 83 (58), 67 (28), 55 (100), 41 (66), 36.5 (metastable).

2-(*tert*-Butylamino)nitroethene (10). From potassium (7.82 g, 0.20 g-atom), *N*-ethylidene-*tert*-butylamine[24] (9.90 g, 0.10 mol), *n*-propyl nitrate (15.8 g, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 150 mL of liquid ammonia, there was obtained a red-brown oil (8.41 g, 58%) which did not crystallize. A 3.31-g portion was chromatographed twice on a 30 × 2.5 cm silica gel column and eluted with ether to afford 1.82 g of a yellow semisolid mixture of **10** (21%) and **5** (10%), as determined by NMR: IR ($CHCl_3$) 3333 (NH) and 1645 cm^{-1} (C=C or C=N); NMR ($CDCl_3$) 1.40 [s, 9, $(CH_3)_3C$], 2.07 (s, 1.0, $C=CCH_3$), 6.52 (d, 0.5, $CH=CHNO_2$), 7.14 [d, 0.35, $CH=C(NO_2)-CH_3$, *J* = 14 Hz], 7.20 (quartet, 0.50, $CH=CHNO_2$, *J* = 14, 6 Hz), and 9.6 ppm (br, 1, NH).

When ethyl nitrate was the nitrating agent, there was obtained after a similar workup **10** (2 g, 13.8%): mp 81–82 °C (hexane); UV λ_{max} (95% C_2H_5OH) 353 nm (log ϵ 4.29) and 230 (3.26); IR ($CHCl_3$) 3257 (NH), 1637 (C=C or C=N), 1353, 1319, and 1232 cm^{-1} (NO_2); NMR ($CDCl_3$) 1.40 [s, 9, $(CH_3)_3C$], 6.50 (d, 1, $CH=CHNO_2$ *J* = 6 Hz), 7.04 (q, 1, $CH=CHNO_2$, *J* = 14, 6 Hz), and 9.5 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 144 (28), 129 (36), 115.5 (metastable), 89 (11), 72 (13), 59 (38), 41 (100); mol wt [$(CH_3)_2CO$] calcd 144.17, found 144.01.

1-(*tert*-Butylamino)-2-nitro-1-butene (6). From potassium (7.82 g, 0.20 g-atom), *N*-butylidene-*tert*-butylamine[20] (12.7 g, 0.10 mol), *n*-propyl nitrate (15.8 g, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 150 mL of liquid ammonia, there was obtained an orange amorphous solid (11.7 g, 68%). Recrystallization from hexane afforded **6** (8.69 g, 51%): pale yellow needles; mp 91.5–92 °C; UV λ_{max} (95% C_2H_5OH) 370 nm (log ϵ 4.13) and 259 (2.58); IR ($CHCl_3$) 3247 (NH), 1646 (C=C or C=N), 1362, 1325, and 1235 cm^{-1} (NO_2); NMR

($CDCl_3$) 1.12 (t, 3, CH_3), 1.37 [s, 9, $(CH_3)_3C$], 2.47 (m, 2, CH_2), 7.05 (d, 0.9, C=CH, *Z* isomer, J = 14 Hz), 8.37 (d, 0.1, C=CH, *E* isomer, J = 14 Hz), and 9.7 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 172 (39), 157 (26), 143.1 (metastable), 116 (8), 101 (29), 72 (18), 57 (100), 41 (36).

1-(*tert*-Butylamino)-2-nitro-1-heptene. From potassium (7.82 g, 0.20 g-atom), *N*-heptylidene-*tert*-butylamine (16.9 g, 0.10 mol), *n*-propyl nitrate (15.8 g, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 100 mL of liquid ammonia, there was obtained an orange waxy solid (11.1 g, 52%). Recrystallization from hexane gave 1-(*tert*-butylamino)-2-nitro-1-heptene (9.78 g, 46%): waxy yellow plates; mp 77.5–78 °C; UV λ_{max} (95% C_2H_5OH) 370 nm (log ϵ 4.20) and 260 (3.04); IR ($CHCl_3$) 3247 (NH), 1650 (C=C or C=N), 1368, 1325, 1238, and 1227 cm^{-1} (NO_2); NMR ($CDCl_3$) 0.90 (t, 3, CH_3), 1.33 (m, 6, CH_2), 1.38 [s, 9, $(CH_3)_3C$], 2.38 (m, 2, CH_2), 6.97 (d, 1, C=CH, *Z* isomer, J = 14 Hz), and 9.6 ppm (br, 1, NH).

1-(*n*-Hexylamino)-2-nitro-1-butene. From potassium (7.82 g, 0.20 g-atom), *N*-butylidene-*n*-hexylamine (15.5 g, 0.10 mol), *n*-propyl nitrate (15.8 g, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 150 mL of liquid ammonia, there was obtained a dark red oil (17.7 g, 76%).

A 2.67-g portion of this oil was chromatographed on a 15 × 2.5 cm silica gel column and eluted with ether. The ether was removed in vacuo and the procedure was repeated to afford 1-(*n*-hexylamino)-2-nitro-1-butene (2.01 g, 67%): light orange, nondistillable liquid; $n^{20}D$ 1.5485; UV λ_{max} (95% C_2H_5OH) 370 nm (log ϵ 3.85) and 244 (3.00); IR ($CHCl_3$) 3247 (NH), 1647 (C=C or C=N), 1362, and 1235 cm^{-1} (NO_2); NMR ($CDCl_3$) 0.85–2.0 (m, 14, CH_2 and CH_3), 2.45 (m, 2, CH_2), 3.42 (m, 2, CH_2), 7.00 (d, 0.9, C=CH, *Z* isomer, J = 14 Hz), 8.31 (d, 0.1, C=CH, *E* isomer, J = 14 Hz), and 9.6 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 200 (36), 185 (45), 154 (19), 129 (20), 112 (35), 72 (56), 55 (42), 43 (100), 41 (70); mol wt [$(CH_3)_2CO$] calcd 200.28, found 200.99.

Nitration of *N*-Cyclohexylmethylidene-*tert*-butylamine. From potassium (7.82 g, 0.20 g-atom), *N*-cyclohexylmethylidene-*tert*-butylamine (**11**, 16.7 g, 0.10 mol), *n*-propyl nitrate (15.8 g, 0.15 mol), and ammonium chloride (11.8 g, 0.22 mol), in 200 mL of liquid ammonia, there was obtained, upon trituration with hexane and filtering, 4.22 g of a yellow-white solid: mp 119–123 °C. A 2.38-g sample was sublimed at 65–70 °C (0.4 mm) to afford a yellow and a white fraction. These were mechanically separated and each fraction was sublimed. The procedure was repeated four times.

Fraction 1 was **1-(*tert*-butylamino)-2-nitro-1-propene** (**5**, 0.36 g, 4%), mp 105–108 °C. The IR, NMR, and mass spectra were identical with those of authentic **5**.

Fraction 2 was **1,1′-bis(cyclohexylmethylidene-*tert*-butylamine)** (**12**, 1.70 g, 18%): colorless needles; mp 128.5–129 °C; IR ($CHCl_3$) 1658 cm^{-1} (C=N); NMR ($CDCl_3$) 1.20 [s, 9, $(CH_3)_3C$], 1.8 (m, 8, CH_2, ring), 2.00 (m, 2, H, axial, ring), and 7.34 ppm (s, 1, N=CH); mass spectrum (75 eV) *m/e* 332 (calcd *m/e* 332); mol wt [$(CH_3)_2CO$] calcd 332, found 320. Anal. Calcd for $C_{22}H_{40}N_2$: C, 79.45; H, 12.12; N, 8.42. Found: C, 78.99; H, 11.92; N, 8.60.

Distillation of the hexane filtrate in vacuo gave a mixture of cyclohexanecarboxaldehyde (0.28 g, 2%) and recovered **11** (3.73 g, 23%) as determined by GLC. Hydrolysis of the mixture in the presence of 2,4-dinitrophenylhydrazine reagent gave cyclohexanecarboxaldehyde dinitrophenylhydrazone, mp 168–169 °C. A mixture melting point determination with authentic cyclohexanecarboxaldehyde dinitrophenylhydrazone gave no depression.

Reaction of *n*-Butylidene-*tert*-butylamine (4) with *n*-Butyllithium. To a stirred solution of *n*-butyllithium (0.11 mol) in 150 mL of hexane at −20 °C, under nitrogen, was added *n*-butylidene-*tert*-butylamine[20] (12.7 g, 0.10 mol). After allowing 0.5 h for anion formation, the reaction mixture was cooled to −70 °C and *n*-propyl nitrate (15.8 g, 0.15 mol) added dropwise to the rapidly stirred solution, while maintaining the temperature below −40 °C (*Caution:* vigorous exotherm). After 0.5 h the nitration mixture was saturated with dry hydrogen chloride at −40 °C to afford a gelatinous suspension. Extracting with chloroform, filtering, and removing the chloroform in vacuo gave a brown resinous material (19.8 g).

A 5.00-g portion was chromatographed on a silica gel column and eluted with ether to afford (*N*-*tert*-butyl)-4-octylamine (**7**, 1.83 g, 40%): colorless crystals; mp 99–101 °C; IR ($CHCl_3$) 1600 cm^{-1} (C=N); NMR ($CDCl_3$) 0.97 (m, 3, CH_3), 1.53 [s + m, 19, $(CH_3)_3C$ and CH_2], 3.0 (br, 1, CH), and 8.9 ppm (br, 1, NH); mass spectrum (75 eV) *m/e* (rel intensity) 185 (8), 170 (33), 142 (94), 128 (100), 86 (81), 72 (85), 52.1 (metastable), 40.5 (metastable).

Reaction of *N*-Butylidene-*tert*-butylamine (4) with Propanal in Potassium Amide–Liquid Ammonia. To a stirred suspension of potassium amide (0.20 mol) in 200 mL of liquid ammonia at −40 °C was added *N*-butylidene-*tert*-butylamine[20] (**4**, 12.7 g, 0.10 mol). After stirring 0.5 h, the reaction mixture was cooled to −55 °C and propanal (5.81 g, 0.10 mol) added during 5 min (*Caution:* exotherm) while maintaining the temperature below −40 °C. After allowing an additional 25 min for reaction, the mixture was acidified with ammonium chloride (11.8 g, 0.22 mol) at −40 °C and the ammonia replaced with absolute ether. The reaction mixture was filtered and the ethereal filtrate carefully concentrated in vacuo to a volume of ~100 mL. The remainder of the ether was removed by distillation through a 40-cm Todd column packed with 0.25-in. glass helices. The residue remaining from the distillation was redistilled in vacuo from solid potassium hydroxide to afford two fractions.

Fraction 1 [1.50 g; bp 35–40 °C (20 mm); $n^{20}D$ 1.4120] consisted of a mixture of **4** (8%) and *N*-propylidene-*tert*-butylamine (5%), as determined by GLC.

Fraction 2 [1.92 g: bp 80–90 °C (10 mm); $n^{20}D$ 1.4659] consisted of at least six high boiling compounds (by GLC). The presence of olefinic protons in the NMR spectrum indicated that these compounds were products of aldol condensation. They were not identified.

Acknowledgment. The support of this investigation by a grant from Eli Lilly and Co. is greatly appreciated.

Registry No.—**4**, 6852-59-1; (*E*)-**5**, 64331-62-0; (*Z*)-**5**, 64331-63-1; (*E*)-**6**, 64331-64-2; (*Z*)-**6**, 64331-65-3; **7**, 64331-66-4; (*E*)-**8**, 64331-67-5; (*Z*)-**8**, 64331-68-6; **10**, 64331-69-7; **11**, 53188-66-2; **12**, 64331-70-0; *N*-propylideneisobutylamine, 6898-80-2; propanal, 123-38-6; isobutylamine, 78-81-9; *N*-heptylidene-*tert*-butylamine, 6852-61-5; heptanal, 111-71-7; *N*-butylidenehexylamine, 64331-71-1; butanal, 123-72-8; hexylamine, 111-26-2; *N*-propylidene-*tert*-butylamine, 7020-81-7; propyl nitrate, 627-13-4; *N*-propylidenepropylamine, 7707-70-2; (*Z*)-1-(propylamino)-2-nitro-1-propene, 64331-52-8; (*E*)-1-(propylamino)-2-nitro-1-propene, 64331-53-9; *N*-propylideneisopropylamine, 28916-23-6; (*Z*)-1-(isobutylamino)-2-nitro-1-propene, 64331-54-0; (*E*)-1-(isobutylamino)-2-nitro-1-propene, 64331-55-1; *N*-propylidenecyclohexylamine, 1195-49-9; (*Z*)-1-cyclohexylamino-2-nitro-1-propene, 64331-56-2; (*E*)-1-cyclohexylamino-2-nitro-1-propene, 64331-57-3; *N*-ethylidene-*tert*-butylamine, 7020-80-6; ethyl nitrate, 625-58-1; (*E*)-1-(*tert*-butylamino)-2-nitro-1-heptene, 64331-58-4; (*Z*)-1-(*tert*-butylamino)-2-nitro-1-heptene, 64331-59-5; (*E*)-1-(hexylamino)-2-nitro-1-butene, 64331-60-8; (*Z*)-1-(hexylamino)-2-nitro-1-butene, 64331-61-9; cyclohexanecarboxaldehyde dinitrophenylhydrazone, 3335-68-0; *tert*-butylamine, 75-64-9; cyclohexanecarboxaldehyde, 62043-61-0.

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Deprotonation of a Hindered Keteniminium Salt[1]

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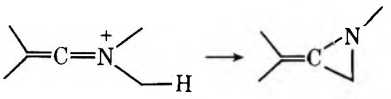
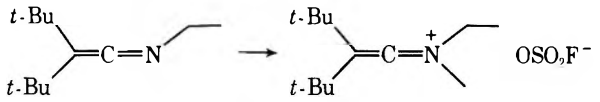
Received July 11, 1977

The synthesis of di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium fluorosulfonate (**2**) is described. This salt owes its unusual stability to the steric bulk of its substituents. Deprotonation of this salt with sodium bis(trimethylsilyl)-amide generated the corresponding azomethine ylide **9**. In the absence of added dipolarophiles, **9** dimerizes to the piperazine **4**. In the presence of norbornene, however, **9** adds in 1,3-dipolar fashion to give **7**. The novel chemical properties of **4**, **7**, and **8** are discussed.

We had previously observed that deprotonation of certain iminium salts could lead to aziridines via ring closure of an intermediate 1,3-dipolar azomethine ylide.[2] Our interest in the synthesis and chemistry of methylene aziridines led us to consider an extension of this reaction to keteniminium salts.



Several procedures were tried in our attempts to prepare keteniminium salts. Although these attempts yielded interesting chemistry, the salts proved much too reactive for general use in our deprotonation studies.[3] One notable exception, di-*tert*-butylketene-*N*-ethyl-*N*-methyliminium fluorosulfonate (**2**), could be prepared in high yield by alkylation of the corresponding ketenimine (**1**) with methyl fluorosulfonate.



1 **2**

Results

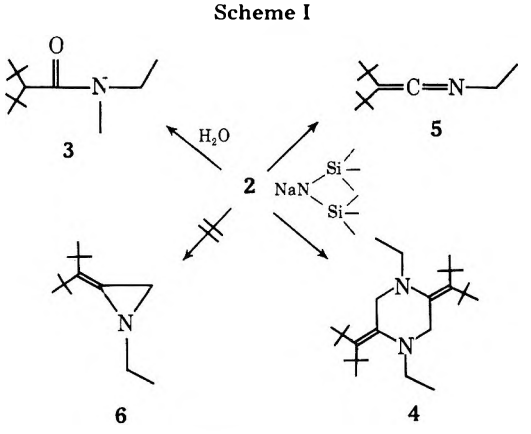
The sterically protected di-*tert*-butylketene-*N*-ethylimine **1** was synthesized from 2,2-di-*tert*-butylacetyl chloride[4] via a conventional procedure (see Experimental Section). The appropriate signals and multiplicities were found in its NMR spectrum. A strong and characteristic infrared maxium at 1998 cm^{-1} assignable to the heterocumulene functionality, C=C=N—, was also observed.[5,6] Attempts to isolate an analytical sample of **1** completely free from di-*tert*-butylacetonitrile[7] either by conventional distillation techniques or by column chromatography resulted in only slight purification. Nevertheless, the alkylation was performed by syringing a twofold excess of methyl fluorosulfonate[8] into a stirred ethereal solution containing ketenimine **1**. Keteniminium fluorosulfonate salt **2** precipitated as a white flocculent solid. This material was determined by spectroscopic analysis to be completely free of nitrile and/or alkylated nitrile by-products.

Keteniminium salt **2** proved to be remarkably stable (mp 224–228 °C with decomposition) considering the known chemistry of other heterocumulenes.[9,10] It is very soluble in polar solvents such as chloroform, ethanol, or water and could be recrystallized from methylene chloride–ether. It was inert toward neutral hydrolysis conditions and it could be recovered unchanged after stirring in water at room temperature for 2 h or more. The infrared spectrum of **2** showed a band of medium intensity at 2000 cm^{-1} which is at somewhat lower frequency than expected for a ketenimine with a positively charged heteroatom. Schiff bases, for example, show appreciable infrared shifts to higher frequency upon protonation or alkylation.[6] Present in the NMR spectrum was a low-field *tert*-butyl signal at δ 1.39 and a deshielded methyl singlet at δ 3.90, as well as the expected ethyl pattern at δ 1.48 (triplet) and 4.11 (quartet). As further structural proof, **2** was hydrolyzed in aqueous base to tertiary amide **3** (Scheme I).

The deprotonation of **2** was performed in benzene using sodium bis(trimethylsilyl)amide as a sterically hindered, nonnucleophilic strong base.[2] Thus, a slurry of **2** in benzene with excess base for 24 h produced the piperazine dimer **4** in 52% yield rather than the intended aziridine **6**. The dimeric structure of **4** was confirmed by its high-resolution mass spectrum which showed a parent ion at *m/e* 390.3977 (calcd for $C_{26}H_{50}N_2$, 390.3973). The NMR spectrum of **4** proved unexpectedly complex. The endocyclic methylene group (H_4, H_5) appeared as a sharp AB quartet (coupling constants and shifts shown in Table I).

The exocylic methylene protons (H_6, H_7) appeared as a quartet of quartets pattern which collapsed to a simple AB system upon spin decoupling of the methyl protons (H_1). The geminal nonequivalence of these protons (H_6, H_7) can be attributed to restricted rotation of the *N*-ethyl groups of **4**.[11] Inspection of molecular models shows extensive steric interaction between the *N*-ethyl substituent and its neighboring *tert*-butyl group.

Scheme I



3 **5** **6** **4**

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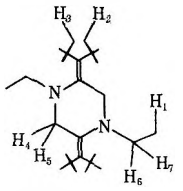
Table I. 100-MHz Proton Spectrum of Piperazine Dimer 4[a]



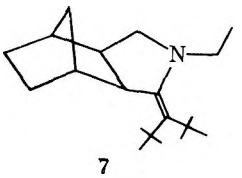
Proton	δ	Multiplicity	J, Hz
H_1	1.07	t	$J_{1,6(7)} = 7$
H_2	1.30	s	
H_3	1.33	s	
H_4	2.60	d	$J_{4,5} = 10$
H_5	3.35	d	$J_{5,4} = 10$
H_6	3.02	d of q	$J_{6,7} = 12$, $J_{6,1} = 7$
H_7	2.72	d of q	$J_{7,6} = 12$, $J_{7,1} = 7$

[a] $CDCl_3$ as solvent.

Although 1,4-cyclohexanedione is known to prefer a nonchair conformation,[12] the NMR pattern displayed by the endocyclic methylene group argues against such a flexible conformation. Molecular models suggest that **4** probably assumes a rigid chairlike conformation in which the two *N*-ethyl groups occupy axial positions. This conformation is consistent with the observed NMR spectrum.

Minor components appeared in the deprotonation product mixture which showed infrared absorption bands of rather weak intensity at ca. 2000 and 1640 cm^{-1}. These were interpreted as arising from dealkylation (to give **5**) and hydrolysis (to give **3**) during the prolonged reaction times. Attempts to encourage ring closure by performing the deprotonation in refluxing benzene again produced piperazine **4** in somewhat higher yield (59%). Deprotonation under the homogeneous conditions of hexamethylphosphoramide (HMPA) resulted in a drastic decrease in dimerization (21%), but only at the expense of hydrolysis to the amide **3** (52%). Further attempts to effect cyclization to **6** were abandoned, and attention was focused on the identity of the supposed "1,3-dipolar" precursor of **4**.

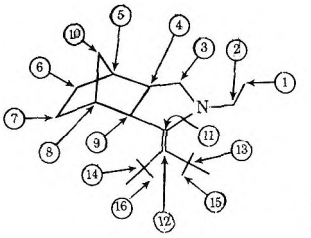
Stereospecific additions to 1,3-dipolarophiles have been of profound importance in establishing the intermediacy of azomethine ylides during the course of aziridine isomerizations.[13] These trapping experiments are now recognized as convincing evidence for the intervention of other 1,3-dipoles as well. Unfortunately, capture of in situ generated 1,3-dipoles by conventional trapping agents was subject to major experimental problems. Most desirable dipolarophiles would hardly withstand the severity of the strongly basic conditions required for dipole formation. Norbornene, however, was found to be inert to the silylamide base under the deprotonation conditions. Treatment of **2** with sodium bis(trimethylsilyl)-amide in the presence of a tenfold excess of norbornene formed the 1:1 adduct **7**. Attempted purification of **7** by



7

short-path distillation resulted in some sample decomposition with no substantial improvement in product quality. Spectroscopic analysis of adduct **7** before distillation revealed a parent ion at *m/e* 289.2761 (calcd for $C_{20}H_{35}N$, 289.2769). Complete analysis of the mass spectrum suggested the presence of at least one other component. The identity and relative percentage of this by-product(s), however, was not determined. NMR spectral analysis showed the expected nonequivalent *tert*-butyl signals at δ 1.35 and 1.50, a methyl triplet at δ 1.00, as well as unresolved methylene and norbornyl multiplets in the range δ 1.0–3.0. ^{13}C NMR (Table II) proved to be helpful in establishing the presence of the olefinic linkage carrying the *tert*-butyl groups. These olefinic carbons appeared as singlets at δ 141.6 and 124.8 downfield from internal Me_4Si and are in agreement with typical shifts for sp^2-hybridized carbons. The assignments made in Table II were based on the multiplicities extracted from single frequency off-resonance decoupling data together with typical chemical-shift values for model norbornyl and pyrrolidine derivatives.[14] The infrared spectrum contained a weak band at ca. 1625^{-1} characteristic of the enamine functionality.[5]

Table II. ^{13}C Chemical-Shift Data for 7 and 8



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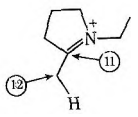

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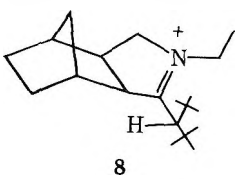
δ[a] (7)	δ[a] (8)	Multiplicity	Assignment
16.0	13.0	q	1
26.2	27.2	t	6
31.1	31.8	q	16
31.6	29.5	t	7
32.6	32.7	q	15
33.6	36.7	s	14
36.0	36.8	s	13
36.7	40.3	d	5
41.1	40.7	d	8
41.8	34.2	t	10
44.3	48.0	t	2
51.1	42.8	d	4
54.6	60.2	d	9
57.4	64.5	t	3
124.8	59.9	s (7) d (8)	12
141.6	195.2	s	11

[a] Chemical shifts are reported downfield from internal Me_4Si with deuteriochloroform as a solvent. Some of these assignments where there are similar shifts and multiplicities may be interchanged.

Interestingly, adduct **7** was derivatized during an attempted purification via column chromatography to a compound which gave an immediate precipitate with silver nitrate. An identical product was formed from hydrochloric acid treatment of **7**. This product is assigned the hydrochloride structure **8** formed



8

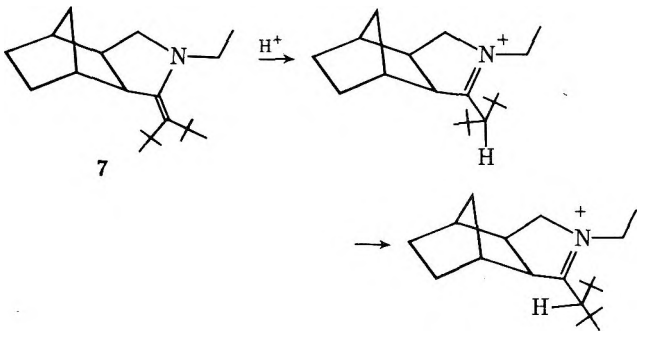
from the protonation of the enamine moiety of **7**.

The NMR spectrum of this derivative was much more informative than that of **7**. The postively charged nitrogen greatly deshields the adjacent exo- and endocyclic pairs of methylene protons while separating the H_{3a} and H_{7a} endo protons by approximately 0.75 ppm. The exo configuration of adduct **7** is based on the ample literature precedent for the preferred exo addition of 1,3-dipoles to norbornene.[13a,13f,14] The ^{13}C spectrum provided valuable structural data. The loss of one olefinic C, the shift of the other to 195, and the multi-

Table III. A Partial Tabulation of Mass Spectral Fragmentations Obtained from 7 and 8

	Rel Intensity, %	
m/e	7	8
289	1.8	2.0
274	2.6	3.3
233	13.5	13.4
232	19.6	23.0
219	17.5	16.7
218	100.0	100.0

Scheme II



7 8

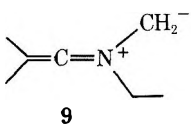
plicity change of C_{12} from a singlet to a doublet are in agreement with C protonation of the enamine. The presence of an infrared band at 1620 cm^{-1} [15] also supports the presence of the iminium functionality (C=N$^+$). High-resolution mass spectrometry failed to show a parent ion at *m/e* 326 for the hydrochloride salt 8. Instead, a pseudo parent ion at *m/e* 289.2763 (calcd for P$^+$ − HCl, 289.2769) was observed. The conspicuous loss of HX from salts has been noted to occur in other systems.[3,16] A tabulation of the major fragmentations of 8 is given in Table III. These are compared with *m/e* values obtained from the mass spectral analysis of freshly prepared 7. The great similarity of these two spectra supports the proposed structural relationship.

The iminium bond of the hydrochloride salt 8 was inert toward attack by a variety of reagents, including methyllithium (addition and/or deprotonation), sodium borohydride (reduction), sodium iodide (dealkylation), and aqueous sodium hydroxide (deprotonation and/or hydrolysis). The unusual proclivity of adduct 7 to scavange HCl and the marked resistance of 8 toward deprotonation warrant further comment.

Analysis of molecular models show that extreme crowding between the *tert*-butyl groups and the norbornyl skeleton in 7 is unavoidable (if approximately normal enamine geometry is maintained). Substantial steric relief, though, is experienced on protonation when rotation of the carbon bearing the *tert*-butyl group assumes a thermodynamically more stable conformation (cf. Scheme II). Conversely, deprotonation of 8 would require rotation of the *tert*-butyl groups into a sterically demanding conformation in which the proton would be in a periplanar arrangement with the p orbital of the iminium bond.

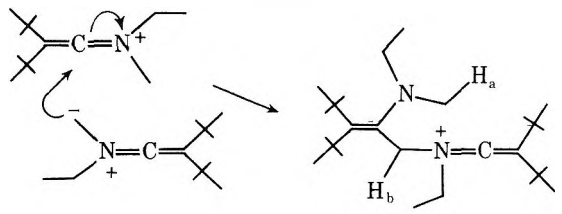
Discussion

The experimental observations of dimerization and stereospecific addition to norborene can be explained in terms of intermediate ylide 9. An alternative stepwise path to dimer



9

Scheme III



10

7 must be considered (Scheme III). Thus, stepwise addition of dipole 9 to iminium salt 2 could yield 10. Although deprotonation of 10 could occur at H_a to give 4 after cyclization, H_a is no longer acidic and it would appear that H_b would be lost with greater ease.[17] We thus prefer the alternative concerted 3 + 3 cycloaddition which has ample literature precedent.

The failure of 1,3 dipole 9 to cyclize to methylene aziridine 6 is surprising.[18] Steric arguments would, if anything, tend to favor 6 over dimer 4. It should be noted, however, that the electrocyclic ring closure proceeds with concomitant destruction of π bonding. It is known the substituents which can stabilize charge facilitate the concerted and reversible thermal ring opening of aziridines. Aziridines which lack such stabilizing substituents tend to sustain carbon–carbon or carbon–nitrogen scission and polymerize when subjected to thermal ring-opening conditions. It is possible, therefore, that the lack of ring closure of 9 results from the lack of groups which would facilitate loss of π overlap.

It should also be noted that the intermediate 9 has a π bond orthoganal to the azomethine ylide π system. The localized π bond is directed toward the opposite partner in the cycloaddition reaction and potentially set up for weak bonding and resultant transition state energy lowering. This rationale is similar to that proposed for 2 + 2 cycloadditions involving ketenes.[21]

Experimental Section

Melting and boiling points are recorded in degrees centigrade and are uncorrected. Melting points were determined with a Thomas-Hoover Unimelt capillary melting-point apparatus using 1.6–1.8 × 90 mm Kimax capillary tubes. Boiling points were determined by conventional distillation techniques or by microcapillary methods. Infrared spectra were recorded on a Perkin-Elmer Model 137 sodium chloride prism spectrometer and calibrated at 1601 cm^{-1} with a polystyrene film. Nuclear magnetic resonance spectra were recorded on a Varian Model A60-A analytical spectrometer for 60-MHz proton spectra and a Varian Model XL-100 spectrometer for 100-MHz proton and proton-decoupled spectra. Carbon-13 nuclear magnetic resonance spectra were obtained from a Varian Model XL-100 spectrometer operating at a probe frequency of 25.16 MHz. All chemical shifts (δ) in designated solvents are reported in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Routine low-resolution mass spectra, exact mass, and molecular weight data were measured on an AEI-MS-30 double-beam spectrometer at an ionizing potential of 70 eV. Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia, and in all cases are in agreement with assigned structures. Where noted, reactions and manipulations of moisture-sensitive compounds were carried out in a Labconco drybox purged with a continuous stream of nitrogen. Solvent evaporations were performed at reduced pressure on a Büchi Rotoavapor-R rotary evaporator equipped with a water aspirator.

***N*-Ethyl-2,2-Di-*tert*-butylacetamide.** Anhydrous ethylamine (15.0 g, 0.333 mol) was placed in a 2 × 30 cm Fischer and Porter Carius tube previously cooled to 0–5 °C with an ice–water bath. 2,2-Di-*tert*-butylacetyl chloride (8.92 g, 46.8 mmol) was added directly to the chilled ethylamine without stirring. The Carius tube was sealed, removed from the ice–water bath, shaken to effect mixing of reagents, and then positioned over a magnetic stirrer where the mixture was stirred for 84 h. The greenish product mixture was evaporated to dryness. The residue was again taken up in chloroform, washed with dilute hydrochloric acid, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent left a pale-yellow solid. Recrystallization from hexane afforded *N*-ethyl-2,2-di-*tert*-butylacetamide

(7.7 g, 82%) as colorless prisms: mp 133–134 °C; IR (KBr) 3230 (N–H, stretch), 1640 (C=O), 1545 cm^{-1} (N–H, bend); NMR ($CDCl_3$) δ 1.10 (s, 18 H), 1.13 (t, J = 7 Hz, 3 H), 1.65 (s, 1 H), 3.23 (q, J = 7 Hz, 2 H), 5.25 (br, 1 H).

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.36; H, 12.56; N, 7.06. Found: C, 72.33; H, 12.63; N, 7.02.

Di-*tert*-butylketene-*N*-ethylimine (1). A solution of *N*-ethyl-2,2-di-*tert*-butylacetamide (2.00 g, 10.1 mmol) in 25 mL of benzene was prepared in a 100-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. Phosphorus pentachloride (2.29 g, 11.0 mmol) was added and the resulting suspension refluxed for approximately 30 min. Benzene and phosphoryl chloride were removed by evaporation at reduced pressure, and the remaining traces of phosphoryl chloride was chased with 20 mL of benzene. The crude imidoyl chloride was treated directly with triethylamine (5.57 g, 7.99 mL, 55.0 mmol) in 50 mL of benzene, and the resulting mixture was refluxed for 2 h. The precipitated triethylamine hydrochloride was removed by suction filtration and the filtrate concentrated at reduced pressure to a brown liquid. Vacuum distillation (Kugelrohr, 40–60 °C/0.25 mmHg) gave di-*tert*-butylketene-*N*-ethylimine (1.60 g) contaminated to the degree of approximately 25% by what appeared to be 2,2-di-*tert*-butylacetonitrile: IR (liquid film) 1998 cm^{-1} (C=C=N); NMR ($CDCl_3$) δ 1.21 (s, 18 H), 1.23 (t, J = 7 Hz, 3 H), 3.39 (q, J = 7 Hz, 2 H); MS m/e calcd for $C_{12}H_{23}N$, 181.1830; found, 181.1827.

Di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium Fluorosulfonate (2). Freshly prepared di-*tert*-butylketene-*N*-ethylimine (1.60 g) was rinsed from the Kugelrohr bulb into a 100-mL round-bottomed flask with 50 mL of anhydrous ether. The flask was then set up for magnetic stirring and protected from atmospheric moisture with a calcium sulfate drying tube. Methyl fluorosulfonate (1.51 g, 1.02 mL, 13.3 mmol) was syringed into the ketenimine solution, and the resulting mixture was stirred at room temperature for approximately 30 min. Precipitation of the keteniminium fluorosulfonate salt as a white flocculent suspension took place within seconds after the introduction of the methyl fluorosulfonate. The colorless solid was collected on a small Büchner funnel by suction filtration and washed several times with anhydrous ether. Recrystallization from chloroform–diethyl ether afforded di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium fluorosulfonate (1.50 g) as a white powder: mp 224–228 °C (dec); IR (KBr) 2000 cm^{-1} (C=C=N); NMR ($CDCl_3$) δ 1.39 (s, 18 H), 1.48 (t, J = 7 Hz, 3 H), 3.90 (s, 3 H), 4.11 (q, J = 7 Hz, 2 H).

***N*-Methyl-*N*-ethyl-2,2-di-*tert*-butylacetamide (3).** Di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium fluorosulfonate (0.250 g, 0.847 mmol) and 15 mL of distilled water were placed in a 25-mL Erlenmeyer flask. The solution was made basic by adding 5 mL of 10% aqueous sodium hydroxide, and the resulting mixture was stirred at room temperature for approximately 10 h. Extraction into three 25-mL portions of diethyl ether followed by drying over anhydrous magnesium sulfate and evaporation at reduced pressure produced *N*-methyl-*N*-ethyl-2,2-di-*tert*-butylacetamide (0.157 g, 87%) as a pale-yellow liquid. Vacuum distillation (Kugelrohr, 100–110 °C/0.3 mmHg) gave an analytically pure sample as a colorless solid: mp 33.5–35.5 °C; IR (CCl_4) 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.07 (s, 18 H), 1.20 (t, J = 7 Hz, 3 H), 2.45 (s, 0.75 H), 2.49 (s, 0.25 H), 2.83 (s, 0.75 H), 3.0 (s, 2.25 H), 3.39 (q, J = 7 Hz, 2 H); MS m/e calcd for $C_{13}H_{27}NO$, 213.2092; found, 213.2092.

Treatment of Di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium Fluorosulfonate (2) with Sodium Bis(trimethylsilyl)amide. *N,N'*-Diethyl-2,5-bis(2,2,4,4-tetramethyl-3-pentylidene)piperazine (4). In a drybox, di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium fluorosulfonate (0.638 g, 2.16 mmol), sodium bis(trimethylsilyl)amide (0.595 g, 3.25 mmol), and 25 mL of dry benzene were placed in a 100-mL round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. The resulting heterogeneous slurry was stirred at room temperature under nitrogen atmosphere for a period of 28 h. During this time, the mixture became somewhat more homogeneous and assumed a bright yellow appearance. The fluorosulfonate salts and excess silylamide base were removed by suction filtration through a bed of Celite, and the clear yellow filtrate evaporated at reduced pressure to a yellow oil (0.406 g). Crystallization from ethyl acetate produced colorless flakes of *N,N'*-diethyl-2,5-bis(2,2,4,4-tetramethyl-3-pentylidene)piperazine in two crops (0.2182 g, 52%): mp 154–156 °C; IR ($CHCl_3$) 1600 cm^{-1} (C=CN); NMR 60 MHz ($CDCl_3$) δ 1.07 (t, J = 7 Hz, 6 H), 1.30 (s, 9 H), 1.43 (s, 9 H), 2.33–3.58 (m, 8 H); NMR 100 MHz ($CDCl_3$) δ 1.07 (t, J = 7 Hz, 6 H), 1.31 (s, 9 H), 1.43 (s, 9 H), 2.60 (d, J_{AB} = 10 Hz, 2 H, endocyclic CH_2), 2.74 (d of q, $J_{A'B'}$ = 11.5 Hz, $J_{H,CH3}$ = 7 Hz, 2 H, exocyclic CH_2), 3.01 (d of q, $J_{A'B'}$ = 11.5 Hz, J_{H,CH_3} = 7 Hz, 2 H, exocyclic CH_2), 3.35 (d, J_{AB} = 10 Hz, 2 H, endocyclic CH_2); NMR ^{13}C ($CDCl_3$) δ 13.0 (q, CH_3CH_3), 33.8 (q, *t*-Bu), 42.5 (t, exocyclic CH_2), 45.2 (t, endocyclic CH_2), 45.2 (t, endocyclic CH_2), 141.3 (s, exocyclic, C=C), 147.1 (s, endocyclic, C=C); MS m/e calcd for $C_{26}H_{50}N_2$, 390.3973; found, 390.3977.

Treatment of Di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium Fluorosulfonate (2) with Sodium Bis(trimethylsilyl)amide in Refluxing Benzene. In a drybox, di-*tert*-butylketene-*N*-ethyliminium fluorosulfonate (0.500 g, 1.69 mmol), sodium bis(trimethylsilyl)amide (0.466 g, 2.54 mmol), and 20 mL of dry benzene were combined in a 100-mL round-bottomed flask containing a small magnetic stirring bar. The flask was removed from the drybox, positioned over a magnetic stirrer, and equipped with a reflux condenser and a nitrogen atmosphere. The reaction mixture was refluxed for 6.5 h before being filtered through a small Büchner funnel containing a bed of Celite. The yellow filtrate was evaporated to an oil (0.404 g), diluted with approximately 8 mL of ethyl acetate, and placed in a refrigerator freezer. After several hours, crystalline flakes of piperazine dimer (0.197 g, 59.7%, mp 154–156 °C) appeared and were collected by suction filtration. The mother liquor was examined spectroscopically and was found by comparison with an authentic sample to contain mostly *N*-methyl-*N*-ethyl-2,2-di-*tert*-butylacetamide.

***exo*-*N*-Ethyl-1-(2,2,4,4-tetramethyl-3-pentylidene)perhydro-4,7-methanoisoindole (7) and *exo*-*N*-Ethyl-1-(2,2,4,4-tetramethyl-3-pentyl)-3a,4,5,6,7,7a-hexahydro-4,7-methano-3*H*-isoindolinium Chloride (8).** Di-*tert*-butylketene-*N*-methyl-*N*-ethyliminium fluorosulfonate (0.400 g, 1.36 mmol), norbornene (1.28 g, 13.6 mmol), and 15 mL of dry benzene were combined in a 50-mL round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube. The flask was transferred to a drybox and positioned over a magnetic stirrer where sodium bis(trimethylsilyl)amide (0.75 g, 4.09 mmol) was added. The resulting suspension was then stirred at room temperature under nitrogen atmosphere for 23 h. The golden reaction mixture was passed through a filter funnel containing a bed of Celite, and the yellow filtrate was evaporated at reduced pressure to remove solvent and excess norbornene. After removing the residual traces of solvent by evaporation at high vacuum, *exo*-*N*-ethyl-1-(2,2,4,4-tetramethyl-3-pentylidene)-perhydro-4,7-methanoisoindole (0.386 g, 98.5%) was obtained as an acid-sensitive pale-yellow oil: IR ($CHCl_3$) 1625 cm^{-1} (C=CN); NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, Me), 1.35 (s, *t*-Bu), 1.50 (s, *t*-Bu), 1.0–3.0 (m, methylene and norbornyl); MS m/e calcd for $C_{21}H_{35}N$, 289.2769; found, 289.2761.

The crude isoindole (7) was diluted with approximately 5 mL of benzene and applied to a neutral alumina column (1.25 × 10 cm) packed in petroleum ether (65–100 °C). Five 40-mL fractions were collected with chloroform and discarded. A sixth and final 40-mL fraction was obtained with anhydrous methanol, evaporated to a golden oil, and then diluted with ethyl acetate which produced colorless platelets of *exo*-*N*-ethyl-1-(2,2,4,4-tetramethyl-3-pentyl)-3a,4,5,6,7,7a-hexahydro-4,7-methano-3*H*-isoindolinium chloride (0.289 g, 65.3%): mp 176–179 °C (dec); IR ($CHCl_3$) 1620 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.25 (s, 9 H), 1.28 (s, 9 H), 1.50–1.80 (br m, 6 H, H_5, H_6, H_8), 1.53 (t, J = 7 Hz, 3 H), 2.50 (br s, 1 H, H_7), 3.00 (s, 1 H, exocyclic CH), 3.43 (br d, $J_{3a,7a}$ = 8 Hz, 1 H, H_{7a}), 4.08–5.18 (m, 4 H, endocyclic and exocyclic CH_2); MS m/e calcd for $C_{20}H_{35}N$, 289.2769; found, 289.2763.

Anal. Calcd for $C_{20}H_{35}N{\cdot}HCl{\cdot}H_2O$: C, 69.82; H, 11.14; N, 4.07. Found: C, 69.84; H, 11.15; N, 4.07.

Registry No.—**1**, 64200-90-4; **2**, 64200-92-6; **3**, 64200-93-7; **4**, 64200-94-8; **7**, 64200-95-9; **8**, 64200-96-0; ethylamine, 75-04-7; 2,2-di-*tert*-butylacetyl chloride, 29571-65-1; *N*-ethyl-2,2-di-*tert*-butylacetamide, 64200-97-1; *N*-ethyl-2,2-di-*tert*-butylacetimidyl chloride, 64200-98-2; 2,2-di-*tert*-butylacetonitrile, 62796-07-0; methyl fluorosulfonate, 421-20-5; norbornene, 498-66-8.

References and Notes

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(8) Methyl fluorosulfonate (Magic Methyl, 97%) was purchased from Aldrich

Chemical Co., Inc. This reagent has been established to be a severe poison. All manipulations were carried out in a well-ventilated hood and protective rubber gloves were worn when making transfers.
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(17) Steric inhibition of deprotonation[2] could inhibit loss of H_b. Inspection of appropriate models suggests that base attack on H_b would not be subject to any severe steric restraints.
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Vinylogous Systems. 4. Mass Spectra of Vinylogous Ureas and Ureides[1]

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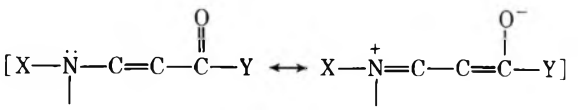
Received June 10, 1977

The mass spectra of 16 acyclic and isocyclic vinylogous ureas **1a** and 18 acyclic, isocyclic, and heterocyclic vinylogous ureides **1b** are reported and discussed. Preferred fragmentation pathways for both **1a** and **1b** are dominated by cleavage at the ends of the conjugated system, with the enaminone core (N—C=C—C=O) being retained within either a charged daughter ion or an ejected neutral fragment. Such decomposition usually furnishes the base peak in the mass spectrum, and is very often a primary step as well.

In continuation of our studies of elongated functional groups in which nitrogen is the electron donor and carbonyl the acceptor, we wish to report the syntheses and mass spectra of some vinylogous ureas **1a**, β-amino α,β-unsaturated amides, and vinylogous ureides **1b**, β-amido α,β-unsaturated amides. Our main goal was to provide a further evidence of the importance of resonance stabilization within the enaminone core of **1**. The competing cross conjugation which exists in **1a–d** is apparently minimal, as shown by spectral results for **1a** (UV[2]), vinylogous imide **1c** (UV,[3] IR,[4] and mass spectra[1]), and vinylogous urethane **1d** (IR[4]).



1a, X = R; Y = NR_2
b, X = RC(O); Y = NR_2
c, X = RC(O); Y = R
d, X = R; Y = OR
e, X = R; Y = R

Electron impact-induced fragmentations of vinylogous amides **1e**[5-7] and imides **1c**[1,8] have been reported, and distinct analogies between the behavior of **1a** and **1e**, and of **1b** and **1c** also, were to be expected. Thus, the formation of a relatively stable β-amino α,β-unsaturated acylium ion from **1a** would be reasonable, although we were unsure whether oxazolium and/or isoxazolium daughter ions would be as important for **1b** as they are in the fragmentation of **1c**. Compounds prepared for the present investigation are collected in Tables I and II.

Experimental Section

Melting and boiling points are uncorrected. Common reagents were freshly distilled (amines from BaO) under a dry atmosphere. Commercial samples of anhydrous alcohol, acrylic anhydride (Aldrich Chemical Co.), and reagent grade acetic anhydride were used. Propiolamide (Terro-Marine Bioresearch) was sublimed under vacuum. Reaction progress and product purity were monitored by thin-layer chromatography. Preparative chromatography was carried out on columns dry packed with Florisil. Solvents were evaporated under reduced pressure on a rotary evaporator with a bath of suitable temperature. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Mass spectra were obtained on either an A.E.I. MS-30 or MS-902 mass spectrometer using a direct-insertion probe under the following conditions: electron voltage 70 eV, ion source temperature 200–250 °C, probe temperature 75–230 °C.[9] Accurate mass measurements were also obtained for compounds **2e, 2h, 2k, 8a–c, 12a, 12n,** and **19a,** as well as for selected peaks of compounds **2d** and **19d.** Infrared spectra were recorded on a Beckman IR-8. Deuteration of compound **12f** was carried out in $CDCl_3$ by shaking with D_2O for 6 h, NMR measurements showing no evidence for exchange except at NH, where it was complete.

Preparation of Compounds. A number of the compounds were synthesized according to the literature, including **2a,**[10] **2b,**[11] **2c,**[12] **2h,**[13] **8d,**[14] **12a,**[15] **12h,**[15] **19a,**[16] and **19b.**[16] Such procedures were also used to prepare many of the new compounds reported in Tables I and II. The following experimental directions are illustrative.

β-Amino-*N,N*-pentamethylenecrotonamide (2d). A solution of piperidine (7.72 g, 0.0907 mol) in dry ether (30 mL) was added dropwise under a dry atomosphere to a stirred solution of diketene (7.63 g, 0.0907 mol) in dry ether (30 mL). The reaction solution was refluxed for 45 min, cooled to ice temperature, and then saturated with NH_3 for 4 h. Removal of the ether left a thick oil which did not solidify in the refrigerator overnight. Using Becker's[17] method, a catalytic amount of NH_4NO_3 was added to the thick liquid, and the mixture was saturated with NH_3 for 5 h at 80 °C. Cooling gave a crystalline mass, which upon recrystallization from ethyl acetate and chromatography (ether) of the mother liquor yielded 12.59 g (83%) of **2d,** mp 78–79 °C. Recrystallization from cyclohexane–ether and subsequent sublimation at 68 °C (0.1 mm) gave pure **2d,** mp 79–80 °C.

2-Aminocyclopentene-1-*N*-ethylcarboxamide (2e). A solution of 2-oxocyclopentane-1-*N*-ethylcarboxamide[18] [4.10 g, 0.0264 mol, bp 102–107 °C (0.5 mm), mp 83–84 °C, lit.[19] mp 84 °C] in absolute ethanol (50 mL) was saturated with NH_3 for 2 h on each of five suc-

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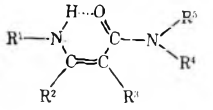
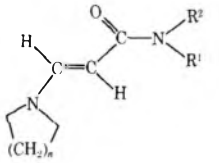
Table I. Vinylogous Ureas



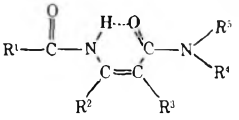
Compd[a]	Registry no.	R^1	R^2	R^3	R^4	R^5	Mp, °C	Yield, %	Recrystn solvent
2a	64163-94-6	H	Me	H	H	H	97-98[b]	82	$CHCl_3$
2b	64163-95-7	H	Me	H	H	Me_2CH	140-142[c]	62	MeCN
2c	59846-47-8	H	Me	H	H	Ph	143-144[d]	76	EtOAc
2d	64163-93-5	H	Me	H	$-(CH_2)_5-$		79-80	83	C_6H_{12}-Et_2O
2e	64163-92-4	H	$-(CH_2)_3-$		H	Et	125-126	70	EtOAc
2f	49786-30-3	H	$-(CH_2)_3-$		H	Ph	200-201 dec[e]	81	MeCN
2g	59846-79-6	H	$-(CH_2)_4-$		H	Ph	108.5-110	92	
2h	64163-96-8	Me_2CH	Me	H	H	Me_2CH	93-95[f]	82	C_6H_{12}
2i	64163-97-9	Me_2CH	$-(CH_2)_3-$		H	Et	111-112	80	C_6H_{12}
2j	64163-98-0	Me_2CH	$-(CH_2)_3-$		H	Ph	121-122	81	$CHCl_3$-Et_2O
2k	64163-99-1	Me_2CH	$-(CH_2)_4-$		H	Et	108-109	84	C_6H_{12}



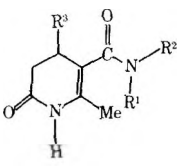
Compd[g]	Registry no.	n	R^1	R^2	Mp, °C	Yield, %	Recrystn solvent
8a	64164-00-7	2	H	H	202-204 dec	97	MeCN
8b	64164-01-8	3	H	H	147-148	97	EtOAc-95% EtOH
8c	64164-02-9	2	$-(CH_2)_4-$		69-72	98	Et_2O-C_6H_{14}
8d	64164-03-0	3	$-(CH_2)_5-$		99-100[h]	61	Et_2O

[a] Satisfactory elemental analysis were obtained for new compounds 2d-g and 2i-k. [b] Lit.[10] mp 98-100 °C. [c] Lit.[11] mp 144-145 °C. [d] Lit.[12] mp 145 °C. [e] Lit.[20] mp 203-205 °C. [f] Lit.[13] mp 90-93 °C. [g] Molecular weight values for new compounds8a-c from exact mass measurements were accurate to within 10 ppm. [h] Lit.[14] mp 99-100 °C.

Table II. Vinylogous Ureides



Compd[a]	Registry no.	R^1	R^2	R^3	R^4	R^5	Mp, °C	Yield, %	Recrystn solvent
12a	64164-04-1	Me	Me	H	H	H	180-181[b]	44	EtOAc
12b	64164-05-2	Me	Me	H	H	Me_2CH	116-118	73	EtOAc-C_6H_{12}
12c	64164-06-3	Me	Me	H	H	Ph	148-149	73	EtOH-H_2O
12d	64163-75-3	Me	$-(CH_2)_3-$		H	Et	110-111	73	H_2O-MeOH
12e	64163-76-4	Me	$-(CH_2)_3-$		H	Ph	101-105	88	MeOH
12f	64163-77-5	Me	$-(CH_2)_4-$		H	Et	103-105	63	EtOAc-C_6H_{12}
12g	64163-78-6	Me	$-(CH_2)_4-$		H	Ph	189-190	68	MeCN
12h	64163-79-7	Ph	Me	H	H	H	148-149[c]	38	MeCN
12i	64163-80-0	Ph	Me	H	H	Me_2CH	148-149	70	EtOAc
12j	64163-81-1	Ph	Me	H	Et	Et	81.5-82.5	51	MeOH
12k	64163-82-2	Ph	Me	H	$-(CH_2)_5-$		110-110.5	65	Et_2O
12l	64163-83-3	Ph	$-(CH_2)_3-$		H	Et	124-125	51	C_6H_{12}-EtOAc
12m	64163-84-4	Ph	$-(CH_2)_4-$		H	Et	143-144	68	EtOAc
12n	64163-85-5	Ph	$-(CH_2)_4-$		H	Ph	255-256 dec	64	$HCONMe_2$



Compd[a]	Registry no.	R^1	R^2	R^3	Mp, °C	Yield, %	Recrystn solvent
19a	63897-27-8	H	H	H	245-246 dec[d]	44	95% EtOH
19b	63897-29-0	H	H	Me	203-204[e]	60	95% EtOH
19c	64163-86-6	H	Me_2CH	H	193-194	35	95% EtOH-H_2O
19d	64163-87-7	$-(CH_2)_5-$		H	117-118.5	47	Me_2CO

[a] Satisfactory elemental analysis were obtained for all new compounds listed in the table. [b] Lit.[15] mp 176-177 °C. [c] Lit.[15] mp 147-148 °C. [d] Lit.[16] mp 241-242 °C dec. [e] Lit.[16] mp 199-200 °C dec.

cessive days. Removal of solvent left a white solid which was redissolved in fresh anhydrous ethanol (30 mL) prior to treatment with NH_3 as above for 2 more days. Freed of solvent, the crude product was recrystallized from ethyl acetate to give 2.86 g (70%) of **2e** as fine white needles, mp 123–126 °C. Vacuum sublimation at 115 °C (0.1 mm) gave the analytical sample, mp 125–126 °C.

2-Isopropylaminocyclopentene-1-*N*-ethylcarboxamide (2i). A mixture of 2-oxocyclopentane-1-*N*-ethylcarboxamide[18] (3.10 g, 0.0200 mol) and isopropylamine (1.77 g, 0.0300 mol) in anhydrous ether (80 mL) was refluxed under a dry nitrogen atmosphere until a light-yellow solution formed (2 days). Removal of solvent followed by recrystallization from cyclohexane yielded 3.12 g (80%) of white needles of **2i**, mp 109–111 °C. Vacuum sublimation at 100 °C (0.1 mm) provided an analytical sample, mp 111–112 °C.

β-Pyrrolidinoacrylamide (8a). A solution of pyrrolidine (1.14 g, 0.0160 mol) in anhydrous ether (15 mL) was added dropwise to a stirred solution of propiolamide (1.00 g, 0.0145 mol, mp 58–60 °C) in ether (15 mL) under dry nitrogen. When approximately one-third of the amine solution has been added, a fine white precipitate formed. After 4 days, 1.98 g (97%) of **8a** was collected as a cream-colored powder, mp 202–204 °C dec (preheated bath). Recrystallization from acetonitrile gave the analytical sample, mp 206–207 °C dec.

β-Acetylamino-*N*-isopropylcrotonamide (12b). A mixture of **2b** (5.68 g, 0.0400 mol) and acetic anhydride (24.5 g, 0.240 mol) was heated to boiling under a dry atmosphere and then allowed to stand at room temperature overnight. Acetic acid and excess anhydride were distilled off under reduced pressure (10 mm) to leave a crystalline residue. Recrystallization of the product from ethyl acetate–cyclohexane yielded white needles (5.35 g, 73%) of **12b**, mp 116–118 °C.

β-Benzoylamino-*N*-isopropylcrotonamide (12i). Benzoyl chloride (4.22 g, 0.0300 mol) was added dropwise to an ice-cold solution of **2b** (4.26 g, 0.0300 mol) in pyridine (20 mL). After standing at room temperature overnight, the reaction mixture was poured into ice water (150 mL). Faintly yellow **12i** (5.15 g, 70%) was collected and, when recrystallized from ethyl acetate, formed white needles, mp 148–149 °C.

6-Methyl-5-pentamethylenecarbamoyl-3,4-dihydro-2-pyridone (19d). A solution of acrylic anhydride (5.10 g, 0.0400 mol) and **2d** (6.73 g, 0.0400 mol) in $CHCl_3$ (100 mL) was refluxed for 1 h. Solvent removal followed by addition of water (100 mL) yielded an aqueous solution. Four extractions of the solution with 100-mL portions of ethyl acetate, followed by removal of organic solvent, provided a gummy residue which soon solidified. Crystallization from acetone led to 4.19 g (47%) of **19d** as white platelets, mp 117–118.5 °C.

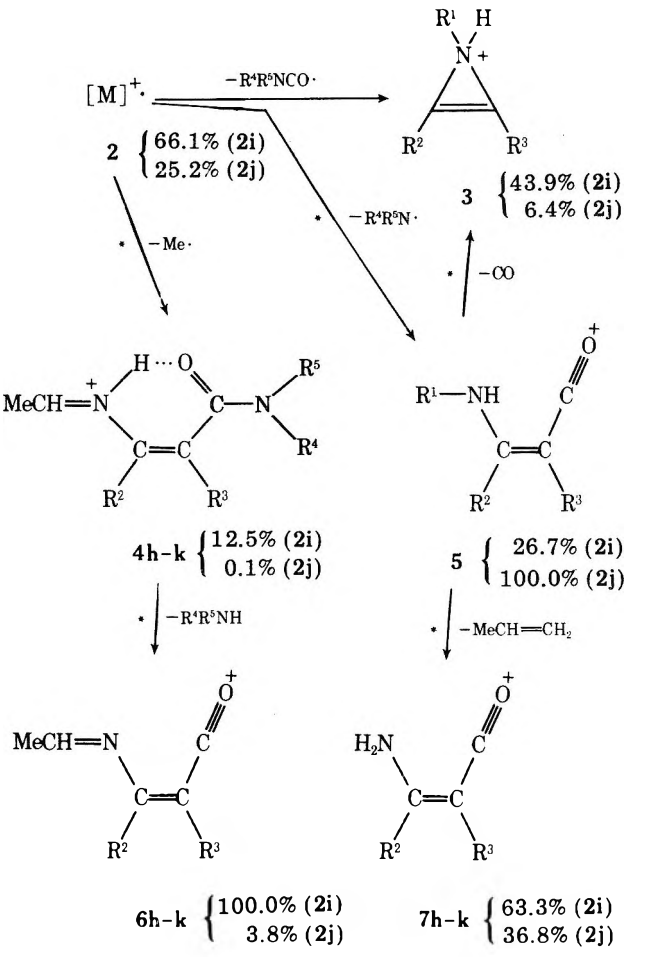
Results and Discussion

Structural assignments for all new compounds are based upon analogy to synthetic procedures and infrared data (1550–1750-cm^{-1} region) in the literature. Infrared assignments for compounds in our collection[21] compare favorably to published results for β-keto amides,[22] vinylogous ureas,[2,14,23] and vinylogous ureides.[16] Conformations and configurations of compounds as shown in the tables are tentative in many instances, and questions of relative stereochemical stabilities will be dealt with in future publications. Fragmentation pathways proposed in Schemes I–IV are supported by appropriate metastable peaks and by selective high-resolution mass measurements, although ion intensities are given for selected compounds only. (See paragraph on supplementary material at the end of the paper.)

Vinylogous Ureas. We turn first to an examination of principal ions in the mass spectra of compounds **2a–k** (Table I) for which the cis configuration is favored by chelation, if not indeed required by a cycloalkene unit. The fragmentation pattern of molecular ion **2** (Scheme I) is strongly influenced by bond cleavage at the carbonyl carbon (as is the case with vinylogous amides[5–7]), the groups (R^1, R^4, and R^5) attached to both nitrogens strongly influencing the relative abundances of the charged species produced upon electron impact.

Thus, the resonance-stabilized β-amino α,β-unsaturated acylium ion **5** shown in Scheme I is the base peak in most instances. Substituent effects are readily apparent, and the exceptional intensity of base peak **5j** (25% of total ion current for m/e >39) is attributed to both the electron-donating power of the isopropyl group (R^1) and to the stability of the neutral

Scheme I



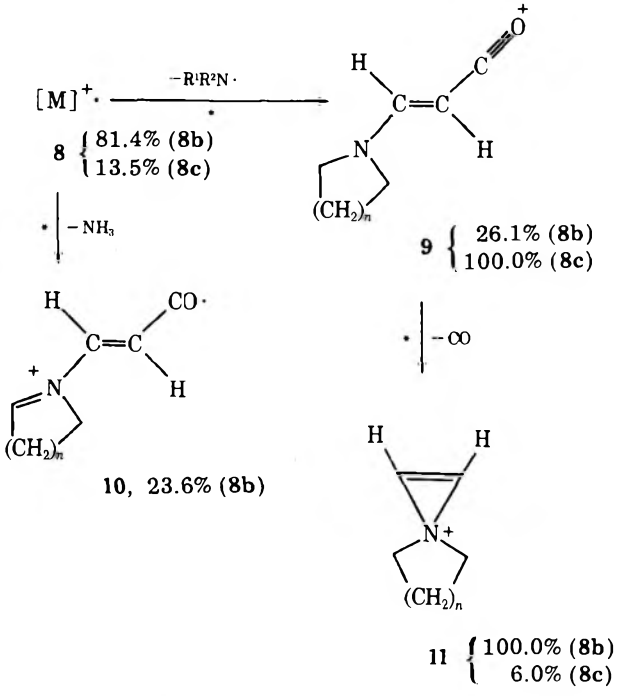
fragment (PhNH·) being expelled during **2j** → **5j**. Loss of propylene from cation **5** yields the abundant acylium ion **7**, whose structure and resonance stabilization is comparable to its progenitor. Another highly conjugated acylium ion, cation **6**, is formed by primary fission of a methyl radical (**2** → **4**), followed by ejection of an amine molecule. As expected, cation **6i** is particularly favored because the competing pathway, carbonyl carbon–nitrogen bond cleavage (**2i** → **5i**), produces the relatively unstable primary amine radical EtNH·.

The mass spectra of trans[24] vinylogous ureas **8a–d** (Table I) were examined next, and the basic fragmentation pattern (see Scheme II) is clearly related to that of Scheme I, as shown in the relative importance of acylium ion **9**. Primary fission adjacent to the enamino nitrogen atom also occurs, our formulation of radical cation **10** being supported by metastable peaks, accurate mass measurements for **8a** and **8b**, and fragmentation modes for vinylogous amides of comparable structures.[5–7] Whereas primary loss of a hydroxyl radical is very important in the mass spectra of appropriate vinylogous amides derived from piperidine,[5,7] we find that both **8a** and **8b** prefer to oust a neutral ammonia molecule.

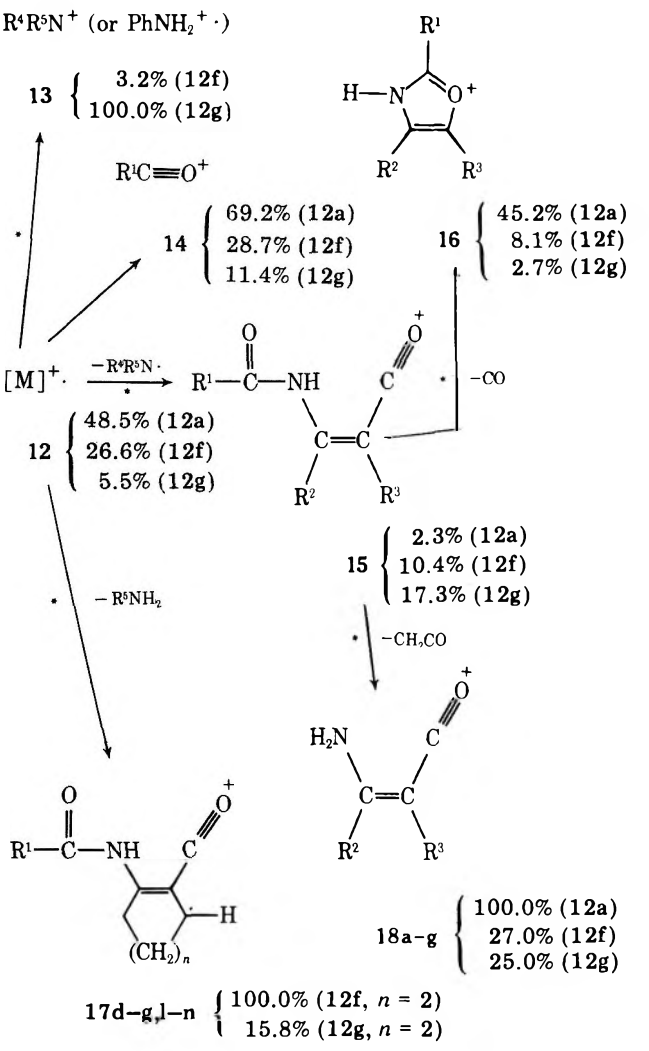
Vinylogous Ureides. Interpretation of mass spectral information for cis compounds **12a–n**[25] (Table II) is reasonably straightforward, and is outlined in Scheme III. The presence of the acyl group R^1CO evidently destabilizes fragment ion **15** (as compared to **5** in Scheme I), and the initial decomposition of vinylogous ureides **12a–n** produces a variety of important charged fragments. Thus, the base peak in the spectra of **12c**, **12e**, and **12g** is the aniline radical cation **13**; for compounds **12h–n** it is the benzoyl cation **14**. Oxazolinium ion **16** is of moderate importance, its abundance ranging from 45.2 (**12a**) to 0.3% (**12c**) of the appropriate base peak.

None of these pathways is particularly favored in the case

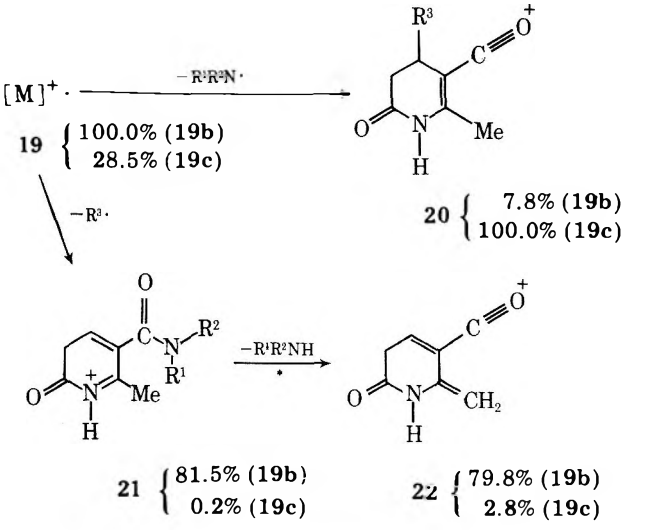
Scheme II



Scheme III



Scheme IV



of **12d** and **12f**. In each instance, the molecular ion expels ethylamine, affording radical cation **17** as the base peak. Removal of an allylic hydrogen atom occurs twice as often at carbon than it does at nitrogen, and the dominant path is depicted in Scheme III. This was established when mass spectra of *N*-deuterated vinylogous ureide **12f**-d_2 and the unlabeled compound were compared.[26] Evidently chelation in **12f**[27] is not strong enough to direct attack exclusively at the ring methylene.

Finally, four heterocyclic trans compounds (Table II) were studied. The decomposition mechanism outlined in Scheme IV for **19a–d** parallels the results of an earlier investigation[8] of 5-acetyl-6-methyl-3,5-dihydro-2-pyridone and some substituted 3,4-dihydro-5-carbethoxy-2-pyridones. Loss of $Me_2CHNH\cdot$ rather than the poorer leaving group $NH_2\cdot$ accounts for the greater abundance of cation **20c** compared to **20b**. Allylic cleavage competes, particularly in **19b** → **21b**, where a methyl radical (rather than H·) is lost. Subsequent expulsion of ammonia generates even electron ion **22b**.

Summary

The electron impact-induced fragmentations of both vinylogous ureas and ureides are dominated by cleavage at the ends of the conjugated system. The enaminone core (N—C=C—C=O), a structural unit which enjoys considerable resonance stabilization, is retained within either a charged daughter ion or an ejected neutral fragment. Such decomposition usually furnishes the base peak in the mass spectrum, and is very often a primary step as well.

Thus, a β-amino α,β-unsaturated acylium ion forms readily from vinylogous ureas, unless expulsion of the relatively unstable neutral fragments $NH_2\cdot$ and EtNH· (which prefer to leave as NH_3 and $EtNH_2$) is required. Vinylogous ureides behave much like vinylogous imides, loss of ketene from *N*-acetyl compounds and formation of $PhCO^+$ from *N*-benzoyl compounds being favorable fragmentation steps. Oxazolium ions are of lesser importance in the mass spectra of vinylogous ureides compared to the imides.

Acknowledgments. The authors are indebted to Professor F. W. McLafferty and Dr. J. W. Sorum of Cornell University for furnishing a number of low-resolution spectra. We also thank Mr. P. J. Taylor and the late Mr. Michael Rix of Imperial Chemical Industries Limited, Macclesfield, Cheshire, England, for high-resolution measurements of selected peaks of **2d** and **19d**, plus spectral results for deuterated **12f**. Financial support from Concordia College and the National Science Foundation (COSIP grant) is gratefully acknowledged.

Registry No.—piperidine, 110-89-4; diketene, 674-82-8; 2-oxocyclopentane-1-*N*-ethycarboxamide, 64163-88-8; isopropylamine, 75-31-0; pyrrolidine, 123-75-1; propiolamide, 7341-96-0; acetic an-

hydride, 108-24-7; benzoyl chloride, 98-88-4; acrylic anhydride, 2051-76-5; 2-oxocyclopentane-1-carboxanilide, 4874-65-1; 2-oxocyclohexane-1-carboxanilide, 51089-06-6; 2-oxocyclohexane-1-*N*-ethylcarboxanilide, 64163-89-9; 1-*N*-morpholinocyclohexene, 670-80-4; ethyl isocyanate, 109-90-0; 3-chloropropenoyl chloride, 3721-36-6; 2-aminocyclohexene-1-*N*-ethylcarboxamide, 64163-90-2; *N,N*-diethylacetoacetamide, 2235-46-3; β-amino-*N,N*-diethylcrotonamide, 64163-91-3.

Supplementary Material Available. Further synthetic details (7 pages) plus amplified mass spectral data and interpretation (16 pages). Ordering information is given on any current masthead page.

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(21) For example, we have made the following spectral correlations ($CHCl_3$ solvent) for the sequences: 2-oxocyclopentane-1-*N*-ethylcarboxamide, 1730 (s, ring C=O) and 1668 cm^{-1} (s, amide C=O); **2e**, 1645 (v s, C=O) and 1610 cm^{-1} (s, C=C); **2l**, 1630 (v s, C=O) and 1580 cm^{-1} (s, C=C); **12d**, 1702 (m, MeC=O), 1643 (v s, EtNHC=O), and 1619 cm^{-1} (s, C=C); **12l**, 1680 (m, PhC=O), 1640 (v s, EtNHC=O), and 1619 cm^{-1} (s, C=C).
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(23) T. Kato, H. Yamanaka, J. Kawamata, and H. Shimomura, *Chem. Pharm. Bull.*, **17**, 1889 (1969).
(24) A trans–cis structure for all four compounds is supported by previous authors,[2,14] and is expected since the cis configuration would not be chelated and is sterically hindered as well.
(25) Acylation of the enamino nitrogen of a cis vinylogous urea should enhance existing chelation when possible in the vinylogous ureide product.
(26) Some reversion of the original deuteration of **12f** occurred in the mass spectrometer and could not be prevented even by deuterating the probe. Correcting for natural isotopic abundances, the actual molecular ion mass ratios for "dideuterio" **12f** were 0.08:0.52:1.00 for *m/e* values 210 (**12f**), 211 (**12f**-d_1), and 212 (**12f**-d_2), respectively. Observed mass ratios of 1.00:1.18:0.13 (corrected as above) for *m/e* values 165 (**17f**), 166 (**15f** and **17f**-d_1), and 167 (**15f**-d_1) respectively, agree quite well with those calculated, assuming the deuterium atoms in a sample of **12f**-d_1 are divided equally between the two nitrogen atoms, and only a statistical preference exists between N–H and C–H cleavage when ethylamine is ejected by molecular ion **12f**.
(27) No irregularities are apparent in the 100-MHZ NMR spectrum of **12f** in $CDCl_3$, and it includes signals at δ 12.7 (s, 1 H, chelated) and 6.10 (t, J = 7 Hz, 1 H).

A New Reaction of Amino Acids: Conversion to Benzoxazoles

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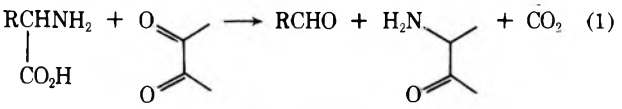
Received April 8, 1977

Reaction of α-amino acids with *o*-benzoquinones of type **3** is unique in that the expected Strecker degradation does not occur. We have observed that a decarboxylative condensation reaction takes place affording benzoxazoles. The new reaction appears to be general for α-amino acids and specific for quinones of type **3**.

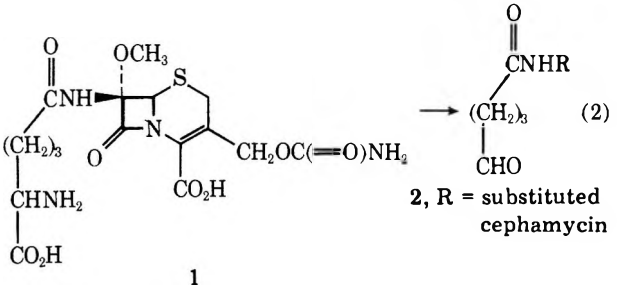
It has been reported that several diones (including *o*-quinones) oxidize α-amino acids to aldehydes while being reduced to α-amino carbonyls[1] (see eq 1). This reaction has been



(1)

termed[1] the "Strecker degradation" in honor of this discoverer.[2]

We were interested in oxidizing the antibiotic α-amino acid **1** to the corresponding aldehyde **2** (eq 2). The Strecker degradation appeared to be the most suitable method since the complexity and sensitivity of **1** warrants mild handling. Furthermore, the use of commercially available 3,5-di-*tert*-butylbzoquinone (**3**) appeared to be the most suitable dione since the steric bulk of the *tert*-butyl groups would prevent undesirable 1,4 addition of the amino acid, and the formation of an aromatic moiety (the reduced α-amino carbonyl now being an *o*-aminophenol) would provide a driving force for the oxidation–reduction process.



(2)

1

2, R = substituted cephamycin

Results and Discussion

Amino acid **1** required 2 equiv of quinone **3** for complete reaction. However, instead of isolating the desired aldehyde **2** and the *o*-aminophenol, the benzoxazole **4** and catechol **5** were obtained (eq 3).

This oxidation reaction appears to be general for α-amino acids since alanine, α-aminoadipic acid, and phenylalanine all yielded the corresponding benzoxazoles[3] when treated with 2 equiv of **3**. The reaction with phenylalanine is complicated by a few minor side reactions; however, fair to good yields of pure products may be isolated by chromatography (see Experimental Section).

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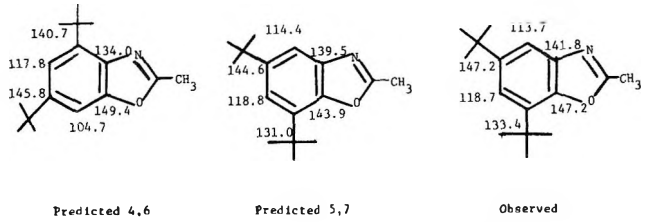
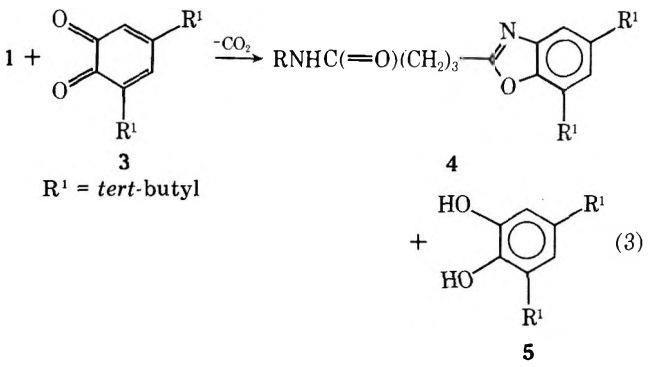


Figure 1. Predicted ^{13}C chemical shift values for 4,6- and 5,7-disubstituted benzoxazoles.[5] Experimental values for **6**.



3 **4**

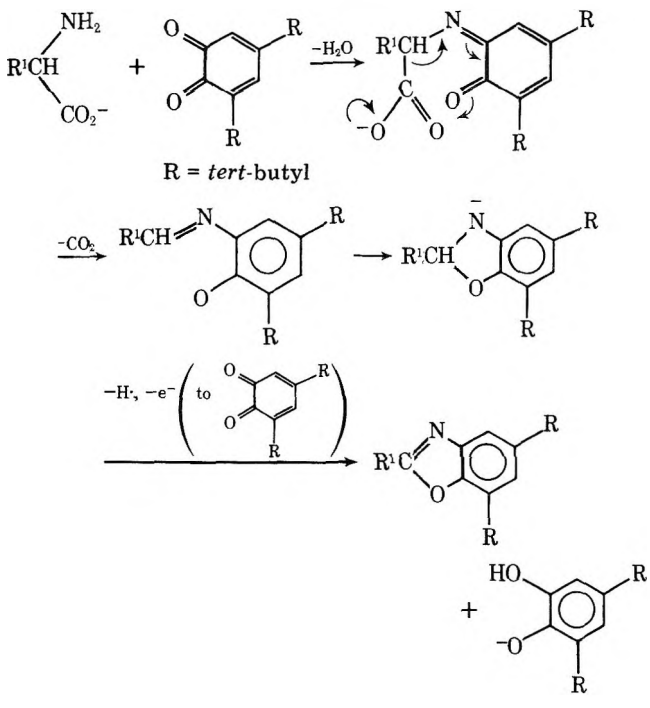
(3)

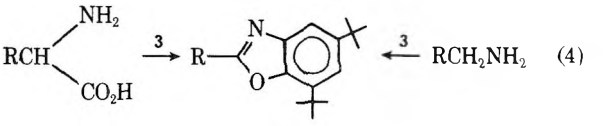
5

This unique reaction appears to be specific for 3,5-disubstituted quinones since complex mixtures were obtained with other diones (2,3-butanedione, 1,2-cyclohexanedione, 1,2-naphthoquinone, 9,10-phenanthroquinone, *o*-benzoquinone, and 4-*tert*-butylbenzoquinone). Furthermore, we were unable to obtain any evidence for oxazole formation with the above diones and alanine. The normal Strecker degradation occurs to some extent with these diones as indicated by the formation of some phenylacetaldehyde when phenylalanine was used. We feel that the propensity for amino acids to react in a 1,4 fashion with unsubstituted quinones removes the possibility for benzoxazole formation, which requires a 1,2 addition. Scheme I provides a suitable explanation for the formation of benzoxazoles from amino acids and o-quinones.

Benzoxazoles have also been prepared from primary amines of the type RCH_2NH_2[4] and quinone **3**. Thus, the reaction described herein establishes an analogy between certain primary amines and α-amino acids when reacted with quinone **3** (see eq 4). When **3** was allowed to react with either alanine or ethylamine, the same benzoxazole was obtained (**6**, R = CH_3) as shown by thin-layer chromatography, mass spectroscopy, and nuclear magnetic resonance spectroscopy, which also proves 5,7 disubstitution (see Figure 1).

Scheme I





6

The reaction may be simplified by using 1 equiv of catechol in the presence of an oxidizing agent. In this manner alanine was converted in good yield to 2-methyl-5,7-di-*tert*-butylbenzoxazole by treatment of its tetraethylammonium salt with 1 equiv each of 3,5-di-*tert*-butylcatechol and manganese dioxide in acetonitrile for 20 min at room temperature. This modification avoids the necessity of performing the quinone and removing the equivalent of catechol formed from the oxidation of the intermediate (see Scheme I). Furthermore, the manganese dioxide is not necessary since stirring an acetonitrile solution of the amino acid salt and quinone in an open vessel for three days affords good yields of substituted benzoxazoles (see Experimental Section).

This new reaction of α-amino acids thus constitutes a viable method for preparing disubstituted (and higher) benzoxazoles.

Experimental Section

2-Methyl-5,7-di-*tert*-butylbenzoxazole (6). A solution of 0.445 g (5.00 mmol) of alanine and 2.95 g (5.00 mmol) of tetraethylammonium hydroxide, 25% aqueous solution, was concentrated at reduced pressure until about 180 mg of water remained. To the concentrate were added 50 mL of acetonitrile and 1.10 g (5.00 mmol) of 3,5-di-*tert*-butyl-o-benzoquinone. The dark colored solution, after being stirred 3 days unstoppered, was concentrated at reduced pressure. The residue was taken up in diethyl ether and extracted twice with H_2O, once with dilute HCl (aqueous), twice with H_2O, and twice with saturated NaCl (aqueous). The ether solution was dried ($MgSO_4$), filtered, and concentrated at reduced pressure to give 1.09 g (80%) of **6**:[3] NMR (acetone-d_6, internal Me_4Si) δ 7.39 (d, J = 2 Hz, 1 H), 7.20 (d, J = 2 Hz, 1 H), 2.55 (s, 3 H), 1.46 (s, 9 H), 1.37 (s, 9 H); mass spectrum, *m/e* 245 (M^+, 17), 230 (1000, 174 (15).

2-Benzyl-5,7-di-*tert*-butylbenzoxazole (7). A solution of 0.540 g (8.88 mmol) of 88.8% sodium methoxide and 1.467 g (8.88 mmol) of β-phenylalanine in 60 mL of methanol was concentrated at reduced pressure to 16 mL. 3,5-Di-*tert*-butyl-*o*-benzoquinone (1.954 g, 8.88 mmol) was added, and the reaction mixture was stirred for 18 h. The reaction was partitioned between ice water and diethyl ether, the layers were separated, and the organic phase was extracted twice with 1 N NaOH, twice with H_2O, and once with saturated NaCl (aqueous). the organic phase was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was taken up in hexane and chromatographed on silica gel (hexane–Et_2O, 20:1) to give 0.451 g (32%) of **7**:[3] NMR (acetone-d_6, internal Me_4Si) δ 7.44 (d, J = 2 Hz, 1 H), 7.26 (broad s, 6 H), 4.25 (s, 2 H), 1.41 (s, 9 H), 1.34 (s, 9 H).

5,7-Bis(*tert*-butyl)-2-benzoxazolylbutanoic Acid (8). To a solution of 243 mg (4 mmol) of 88.8% sodium methoxide and 322 mg (2 mmol) of aminoadipic acid in 10 mL of methanol was added 441 mg (2 mmol) of 3,5-di-*tert*-butyl-*o*-benzoquinone. After 15 min, the dark blue solution was concentrated at reduced pressure. The residue was partitioned between ice water and diethyl ether, the layers were separated, and the aqueous phase was further extracted until the ether layer was colorless. The aqueous phase was adjusted to pH 2.5 and extracted twice with diethyl ether. The latter ether extracts were dried ($MgSO_4$), filtered, and concentrated at reduced pressure to afford 330 mg (52%) of **8**:[3] NMR (acetone-d_6, internal Me_4Si) δ 7.50 (d, J = 2 Hz, 1 H), 7.28 (d, J = 2 Hz, 1 H), 3.69 (s, 3 H), 2.99 (broad t, J = 7 Hz, 2 H), 1.90–2.60 (complex m, 4 H), 1.45 (s, 9 H), 1.34 (s, 9 H); mass spectrum, *m/e* 331 (M^+, 14), 316 (22), 299 (22), 258 (100), 232 (45).

7-[5,7-Bis(*tert*-butyl)-2-benzoxazolyl]butyramido-3-hydroxymethyl-7-methoxy-3-cephem-4-carboxylic Acid Carbamate (4). A solution of 1.22 g (20 mmol) of 88.8% sodium methoxide in 150 mL of methanol was cooled to −5 °C and charged with 10.0 g (20

mmol) of 1. Upon dissolution, 4.41 g (20 mmol) of 3,5-di-*tert*-butyl-*o*-benzoquinone was added, the reaction stirred 1 h, an additional 4.41 g (20 mmol) of the quinone added, and stirring continued for 30 min. The reaction was partitioned between ice water and diethyl ether, the pH was adjusted to 8, the layers were separated, and the aqueous phase was extracted three more times with ether. The combined ethyl acetate extracts were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to yield 8.07 g (67%) of 4:[3] NMR (acetone-d_6, internal Me_4Si) δ 8.27 (broad s, 1 H), 7.48 (d, J = 2 Hz, 1 H), 7.28 (d, J = 2 Hz, 1 H), 5.91 (broad s, 2 H), 5.12 (s, 1 H). 4.86 (AB center, J = 13 Hz, 2 H), 3.82 (s, 3 H), 3.48 (broad s, 5 H), 3.07 (broad t, 2 H), 2.16–2.75 (complex m, 4 H), 1.47 (s, 9 H), 1.35 (s, 9 H); mass spectrum (methyl ester), *m/e* 616 (M^+, 11), 615 (26), 555 (61), 554 (100).

Registry No.—1, 64162-09-0; 3, 3383-21-9; 4, 64130-72-9; 6, 64130-73-0; 7, 64147-38-2; 8, 64130-74-1; alanine, 56-41-7; β-phenylalanine, 63-91-2; aminoadipic acid, 542-32-5.

References and Notes

(1) A. Schöenberg, R. Moubasher, and A. Mostafa, *J. Chem. Soc.*, 176 (1948), and references therein.
(2) A. Strecker, *Justus diebigs Ann. Chem.*, **123**, 363 (1862).
(3) All products were in agreement with ^1H and ^{13}C NMR as well as combustion analyses and mass spectroscopy.
(4) E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.*, **91**, 1429 (1969). For a list of other methods available for the formation of benzoxazoles see J. W. Cornforth, in "Heterocyclic Compounds", Vol. V, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, Chapter 6.
(5) The ^{13}C NMR chemical shifts and ^1H–^{13}C coupling constants of **6** allow unequivocal assignment of the substitution pattern. Although substituent effects are not strictly additive, especially when ortho groups are present, the predicted chemical shifts using benzoxazole and *tert*-butylbenzene as models correlated well for a 5,7-disubstituted benzoxazole when used in conjunction with ^1H–^{13}C coupling data. Long-range ^1H–^{13}C coupling constants can be structurally useful especially in aromatic systems where the most significant long-range coupling is via a three-bond pathway.[6] In **6**, the aromatic carbons bearing hydrogen (113.7 and 118.7 ppm) can easily be determined from the large one-bond couplings, and they each exhibit a single three-bond coupling. The carbon resonanances at 147.2 and 133.4 ppm must be assigned to those bearing *tert*-butyl groups, due to long range couplings with the *tert*-butyl hydrogens. Of the two remaining aromatic signals, the one at 141.8 ppm shows no long-range coupling, while the signal at 147.2 ppm is a triplet ($J \cong 10$ Hz), demanding two ring hydrogens which are at a distance of three bonds. The predicted chemical shift values (see Figure 1) clearly support the 5,7 isomer while ruling out 4,6 disubstitution.
(6) (a) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 2967 (1967); (b) L. Ernst, V. Wray, V. A. Chertkov, and N. M. Sergeyev, *J. Magn. Reson.*, **25**, 123 (1977).

Photoproducts of Thymine and Uracil. Syntheses of the Four Bipyrimidine Combinations

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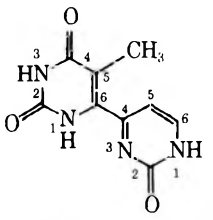
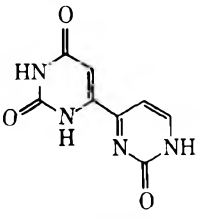
Received June 27, 1977

Convenient first syntheses have been devised for the following bipyrimidines: 6-(2-hydroxypyrimidin-4-yl)thymine, Thy(6-4)Pyo (1); 6-(2-hydroxypyrimidin-4-yl)uracil, Ura(6-4)Pyo (2); 6-(2-hydroxy-5-methylpyrimidin-4-yl)thymine, Thy(6-4)m^{5}Pyo (3); and 6-(2-hydroxy-5-methylpyrimidin-4-yl)uracil, Ura(6-4)m^{5}Pyo (4). The first three of these are among the non-cyclobutane photoproducts resulting from DNA or from frozen aqueous solutions of thymine, thymidine, uracil, or uridine under appropriate conditions. The synthetic methodology involved (1) the combination of 6-lithiopyrimidines with β-alkoxyacroleins, (2) oxidation to the corresponding masked β-dicarbonyl intermediates, (3) condensation of these with guanidine carbonate to form substituted aminobipyrimidines, and (4) diazotization and hydrolysis to furnish the desired products 1–4. The spectroscopic properties, especially the ultraviolet excitation and fluorescence emission, are of special interest within the series and in comparison with the photoproducts of natural origin.

Considerable interest has been displayed in the isolation and identification of photoproducts of DNA as a means of investigating possible photobiological implications. Along with the familiar pyrimidine photodimers of the cyclobutane structure,[1] a series of bipyrimidine photoproducts has been accumulated by Wang and Varghese, exemplified by formulas 1–3.[2] (As drawn, these formulas are not intended to portray a preferred torsional geometry.) The first of these, Thy(6-4)Pyo (1),[3] was identified as a product from the trifluoroacetic acid hydrolysates of DNA irradiated with far-UV light[4–6] and from photolysis of a frozen solution of thymine and uracil.[7] Ura(6-4)Pyo (2) was isolated from the UV irradiation of uracil in frozen aqueous solution[8] and from the acid hydrolysates of uridine irradiated in frozen aqueous solution.[9] Thy(6-4)-m^{5}Pyo (3) was obtained from the UV irradiation of frozen solutions of thymine[10,11] and of thymidine,[12] followed by acid treatment.



1, Thy(6-4)Pyo



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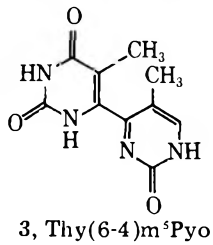
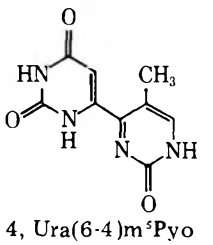


3, Thy(6-4)m^{5}Pyo



4, Ura(6-4)m^{5}Pyo

As part of our continuing interest in the structure determination and synthesis of nucleic acid radiation products,[13–17] we have devised unequivocal syntheses of compounds 1–3 which also provide independent confirmation of their assigned structures. We have also synthesized Ura(6-4)m^{5}Pyo (4) as a potential photoproduct which is theoretically accessible by a photoadduction pathway similar to that suggested for Ura(6-4)Pyo.[9]

An examination of the literature discloses several synthetic routes to bipyrimidines. Symmetrical 2,2′-, 4,4′-, and 5,5′-bipyrimidines have been obtained via an Ullmann or a Busch coupling reaction.[18,19] Symmetrical 4,4′- and 5,5′-bipyrimidines have also been prepared via construction of the carbon backbone followed by condensation with 2 equiv of a urea derivative.[20–23] Unsymmetrical 2,2′- and 2,4′-bipyrimidines

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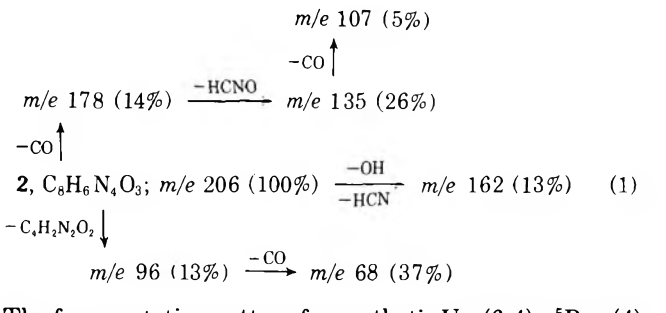
were obtained via the condensation of β-dicarbonyl compounds with 2- or 4-amidinopyrimidines.[24] 5-Lithiopyrimidines were found to undergo self-reaction to form 4,5′-bipyrimidines,[25] with attendant restriction of the substitution pattern in the two rings.

Recent work in our laboratory has demonstrated the applicability of methods employing the attachment of a carbonyl backbone for a second pyrimidine ring to an existing pyrimidine ring.[15] This route was adopted in the present work. In outline, it was envisaged that the ring closure of a β-alkoxy(α-alkyl)acryloyl moiety with guanidine[26] could lead to bipyrimidines that were two simple steps removed from the desired products. The major synthetic problem thus involved the attachment of a masked β-dicarbonyl precursor to the 6 position of an appropriately substituted pyrimidine ring. The approach through a combination of 6-lithiopyrimidines[27] with β-alkoxyacrylates[28] was not pursued because of anticipated difficulties with a competing Michael reaction or a diaddition of the lithio derivative. Such difficulties could be avoided through reaction of the readily available β-alkoxyacroleins with the 6-lithiopyrimidines and subsequent oxidation of the intermediate carbinols.

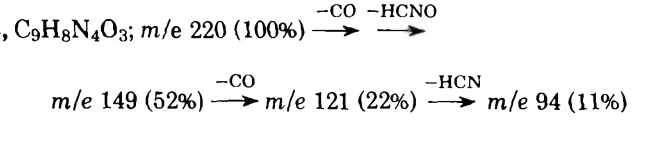
Langley[27] previously synthesized 6-bromo-2,4-diethoxypyrimidine (4-bromo-2,6-diethoxypyrimidine, **6a**) from 2,4,6-tribromopyrimidine (**5a**) and described conditions for the generation of the corresponding lithio derivative by halogen–metal interchange using *n*-butyllithium. Using similar conditions, we obtained 6-bromo-2,4-diethoxy-5-methylpyrimidine (**6b**) from 5-methyl-2,4,6-tribromopyrimidine (**5b**) and likewise observed halogen–metal interchange with *n*-butyllithium at low temperature. Each of the two 6-lithiopyrimidines was treated separately with β-ethoxy-α-methylacrolein (**7a**)[29] and β-benzyloxyacrolein (**7b**)[30,31] to yield the corresponding carbinol derivatives **8** after quenching with 20% aqueous NH_4Cl solution. The pyrimidinecarbinols **8** were oxidized with activated MnO_2[32] to the corresponding acryloylpyrimidines **9**, and these were condensed with guanidine carbonate to form the substituted aminobipyrimidines **10**. It was unnecessary to isolate the intermediates **8** and **9** in pure form, although this was done in the **a** series as a control. Diazotization of compounds **10a–d** followed by hydrolysis of the intermediates **11a–d** furnished the desired products **1–4**.

At every stage in the unequivocal synthetic process the compounds were fully characterized by elemental analyses and by ultraviolet, nuclear magnetic resonance, and mass spectrometry. The properties of the final products could be compared with those previously reported for the corresponding photoproducts. The mass spectra determined at either 70 or 10 eV showed a predominant molecular ion for **1–4**. The fragmentation pattern for Thy(6-4)Pyo (**1**) matched very closely the fragment ions and relative intensities in the spectrum of the photoproduct as reported by Fenselau and Wang.[33] The same was generally true for the sample of Thy(6-4)m^{5}Pyo (**3**) from synthetic and photolytic sources. The fragmentation pattern for synthetic Ura(6-4)Pyo (**2**) exhibited parallel behavior to the fragmentations recorded for **1** and **3**, as shown in eq 1.



(1)

The fragmentation pattern for synthetic Ura(6-4)m^{5}Pyo (**4**) was of interest vis-à-vis that of the isomeric monomethyl Thy(6-4)Pyo (**1**)[33] since neither exhibited an M − 15 peak, whereas the dimethyl compound Thy(6-4)m^{5}Pyo (**3**) lost a methyl radical. The major fragmentation pathway that we observed at 10 eV for Ura(6-4)m^{5}Pyo (**4**) is shown in eq 2.



(2)

The pair of monomethyl isomers **1** and **4** provided checks for the internal consistency of the NMR assignments throughout the synthetic series **1–4**. The NMR data for the synthetic products **1–3** were consistent with the published proton chemical shifts for the photoproducts if a correction

Table I. Corrected Fluorescence Data[a]

Compd	Registry no.	pH	Fluorescence excitation, nm	Fluorescence emission, nm[b] λ_{max}	$\lambda + \frac{1}{2}$	$\lambda - \frac{1}{2}$	Φ[c]
10a	64188-72-3	7.4	317, 278	465	522	421	0.20
b	64188-73-4	7.4	300, 272 sh	438	505	397	0.065
c	64188-74-5	7.6	312	445	500	407	0.10
d	64188-75-6	7.6	308, 275	435	505	393	0.11
11a	64188-76-7	7.6	328, 270	475	552	415	0.049
b	64188-77-8	7.7	320, 278 sh	445	525	390	0.087
c	64188-78-9	7.8	340 sh, 315	427	480	392	0.067
d	64188-79-0	7.5	310, 277 sh	405	454	373	0.045
4	64188-80-3	9.1	330, 277	513	598	454	0.015[d]
		9.1	330, 277	513	587	459	0.029[e]
1	18694-06-9	9.1	315	484[f]	551	430	0.016
2	35612-19-2	8.9	335, 303	471[g]	552	411	0.032
3	20545-68-0	8.8	315, 270	513[h]	597	450	0.014

[a] In water at 300 K. [b] Wavelengths representing half-heights on each side of the maximum are given. [c] Based on $\Phi = 0.70$[38] for quinine sulfate in 0.1 N H_2SO_4. [d] Excitation at 325 nm. [e] Excitation at 280 nm. [f] λ_{max} 456 nm reported.[36] [g] λ_{max} 444 nm reported.[36] [h] λ_{max} 387 nm reported.[36]

factor was applied to the latter, as had been shown to be necessary in other analogous comparisons.[17,34,35]

The ultraviolet absorption spectra of the four precursors represented by formula **10** and determined at the pH of their solutions in water and in strong acid are sufficiently complex so that unperturbed transitions are not readily assignable. The probability of more coplanarity (two coplanar conformations are possible) being achieved in **10c** than in **10d** is reflected in the molar extinction coefficients and in the wavelengths of the absorption maxima. The ring to which the methyl group is attached, i.e., its position in the monomethyl isomers **10a** and **10b**, has a greater influence than can be accounted for simply by the steric hindrance of one *o*-methyl group compared with two or none. Similar statements can be made for the set of precursors **11**. As for the final products, Hauswirth and Wang[36] have discussed the ultraviolet absorption spectra of compounds **1–3**. A comparison of the spectra of **1** with those of its position isomer **4** indicates that such discussion should take into consideration additional factors such as tautomeric forms, coplanar conformations, and ground-state and transition dipoles, as well as torsional angles relating to simple biphenyls.

The precursors **10** and **11** are all fluorescent, with emission maxima ranging from 405 to 475 nm and quantum yields ranging from 0.04 to 0.20. No consistent pattern over the dual **a–d** series was readily discernible. The data obtained at 300 K in water are assembled in Table I, along with the excitation, emission, and fluorescence yield characteristics of the highly purified, synthetic, bipyrimidines **1–4**. The corrected fluorescence excitation maxima match well with those reported by Hauswirth and Wang[36] for the photoproducts **1–3**. Our corrected emission maxima for **1** and **2** show some discrepancy (+ 27–28 nm) from those reported. The main point of difference is that we observe a fluorescence emission maximum at 513 nm for Thy(6-4)m^{5}Pyo (**3**) in place of the reported 387-nm value.[36] Since no synthetic precursor of **3** exhibits a fluorescence maximum at such long wavelength, since great care was taken in its purification, and since the determination was readily duplicated, we have confidence in the 513-nm value. Moreover, the fluorescence emission maximum observed for Ura(6-4)m^{5}Pyo (**4**) was 513 nm upon excitation at either 227 or 330 nm. As in the case of excitation, there are too many variables to be considered to define the relaxed fluorescing states (at 300 K) in simple terms. The quantum yield of fluorescence was greatest (0.032) for the unmethylated compound **2**, and the quantum yields for the mono- and dimethylated compounds **1**, **4**, and **3** were comparable and approximately half this value (Table I). Location of the methyl group on the pyrimidone ring, as in Ura(6-4)m^{5}Pyo (**4**) and in its precursors **10a** and **11a**, had the greatest effect on the fluorescence properties. Accordingly, the data for compound **4** must be included in any rationalization of the absorption and emission properties of the photoproduct series **1–3** recognized at this time.

Finally, in this work we have provided "improved methods" for preparing the photoadducts of thymine and uracil "in sufficient quantities for studying their possible biological importance." [2] The biological role of products such as **1–4** is not yet clear; the data permit the interpretation that either such photoproducts (i.e., from DNA) are not lethal or that they are lethal but can be repaired under certain conditions.[37] Compounds **1–4** showed no antibacterial activity at 0.1 mg/mL against *B. subtilis*, *E. coli*, and *P. atrovenatum* and no bacterial mutagenic activity in the Ames test.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian A-60, EM-390, or HA-100 spectrophotometers using tetramethylsilane as an internal standard. Mass spectra were run on a Varian MAT CH-5 spectrometer (10 and 70 eV), coupled with a 620i computer and a STATOS recorder. Ultraviolet absorption spectra were obtained on a Beckman Acta M VI spectrophotometer. Corrected fluorescence emission and excitation spectra were measured on a Spex Fluorolog spectrofluorometer. Microanalyses were performed by Mr. Josef Nemeth and his staff, who also weighed samples for quantitative ultraviolet absorption studies. Thin-layer chromatographs were run on EM silica gel f-254 plates (thickness, 0.25 mm).

5-Methyl-2,4,6-tribromopyrimidine (5b). A mixture of phosphorus oxybromide (69.6 g, 0.24 mol), 5-methylbarbituric acid[39] (8.24 g, 0.058 mol), *N,N*-dimethylaniline (16 mL), and toluene (100 mL) in a 500-mL flask was heated at reflux for 5 h. The organic layer was separated, washed with H_2O, dried, and concentrated in vacuo to yellow solid **5b** (10 g, 52% yield). An analytical sample was obtained by recrystallization from absolute ethanol: mp 136–137.5 °C; NMR ($CDCl_3$) δ 2.52 (s, 3, CH_3); MS *m/e* (rel intensity) 328 (37), 330 (100), 332 (99), 334 (53).

Anal. Calcd for $C_5H_3Br_3N_2$: C, 18.14; H, 0.91; N, 8.47. Found: C, 18.35; H, 0.90; N, 8.51.

6-Bromo-2,4-diethoxy-5-methylpyrimidine (4-Bromo-2,6-diethoxy-5-methylpyrimidine, 6b). After the addition of **5b** (11.9 g, 0.036 mol) to benzene (40 mL) and stirring until dissolution was complete, absolute ethanol (35 mL) was added, and the reaction flask was cooled to 5 °C. During the next 60 min a sodium ethoxide solution generated from sodium (1.65 g, 0.072 g-atom) in absolute ethanol (35 mL) was dripped in, and the resulting mixture was stirred overnight. Following sodium bromide precipitation through the addition of anhydrous ethyl ether (50 mL), the mixture was filtered with the aid of additional ether (3 × 15 mL). Concentration of the filtrate in vacuo

left a white solid which was treated with anhydrous ethyl ether (100 mL) and then refiltered in order to remove residual salt. The removal of the filtrate solvent provided a white solid product (8.5 g, 91% yield). From examination of the MS, NMR, and microanalytical data, it was concluded that the reaction product was a mixture of **6b** and the isomeric 2-bromo-4,6-diethoxy-5-methylpyrimidine in a relative proportion of 77:23. Repeated fractional crystallization from 50% aqueous ethanol led to an enrichment of the major isomer **6b** to a purity of >98% (by NMR): 4.16 g, 44% yield; mp 75–76 °C; NMR ($CDCl_3$) δ 1.41 (t, J = 7 Hz, 6, OCH_2CH_3), 2.17 (s, 3, 5-CH_3), 4.42 and 4.48 (q, J = 7 Hz, 2 each, OCH_2CH_3); MS m/e 262, 260 (M^+).

Anal. Calcd for $C_9H_{13}BrN_2O_2$: C, 41.39; H, 5.02; N, 10.73. Found: C, 41.29; H, 4.94; N, 10.63.

That the structure of the isolated major isomer was in fact **6b** was proven through the following procedure. The major isomer (273 mg, 1.05 mmol), dissolved in freshly distilled THF (10 mL), was cooled to −100 °C under a positive nitrogen atmosphere. A dry ice cooled solution of n-butyllithium (1 mL of a 2.4 M solution in hexane, 2.4 mmol) was added to the mixture of THF and precipitated reactant, and the resultant reaction mixture was warmed quickly to −65 °C. At this temperature, an orange homogeneous solution resulted, and the cooling bath was replaced. After 20 min of stirring, the reaction solution was inversely quenched with a mixture of ethyl ether (50 mL) and a 20% aqueous NH_4Cl solution (50 mL). Following the extraction of the aqueous layer with ethyl ether (2 × 50 mL), the organic layers were combined, dried, and concentrated in vacuo to an oil (180 mg, 94%). Analyses of the product via NMR, TLC, and MS matched in all respects an authentic sample of 2,4-diethoxy-5-methylpyrimidine.

2,4-Diethoxy-6-(1-ethoxy-3-hydroxy-2-methylpropen-3-yl)pyrimidine (8a). A solution of 6-bromo-2,4-diethoxypyrimidine (4-bromo-2,6-diethoxypyrimidine, **6a**)[27] (2.0 g, 8.1 mmol) in freshly distilled THF (50 mL) was cooled to −100 °C under a positive nitrogen pressure. A solution of n-butyllithium (3.7 mL of a 2.4 M solution in hexane, 8.9 mmol) cooled in dry ice was added at such a rate that the internal temperature did not exceed −90 °C. The pyrimidine solution was stirred for 5 min, and a solution of β-ethoxy-α-methylacrolein (**7a**,[29] 1.39 g, 12.25 mmol) in THF (5 mL) was added over a 15-s interval. The solution was stirred at −70 °C for 50 min and then allowed to warm to −20 °C over the next 25 min. The reaction was quenched with a mixture of 50 mL of Et_2O and 75 mL of a 20% aqueous NH_4Cl solution. After separation of the organic layer, the aqueous layer was extracted with 50 mL of Et_2O, and the ether extracts were combined and dried over magnesium sulfate. After filtration, the solvent was removed in vacuo to leave a light orange oil. Addition of 25 mL of petroleum ether and refrigeration at −20 °C for 12 h afforded white crystals (0.95 g) which, on washing with excess petroleum ether, proved to be analytically pure. Removal of the petroleum ether in vacuo, addition of 25 mL of pentane, and refrigeration at −20 °C provided additional, slightly yellow crystals: 0.26 g, total yield 53%; mp 61–62.5 °C; NMR ($CDCl_3$) δ 1.27, 1.37, and 1.44 (t, J = 7 Hz, 3 each, OCH_2CH_3), 1.46 (d, J = 1 Hz, 3, $=CCH_3$), 4.2 (br s, 1, CH–OH), 3.85, 4.39, and 4.43 (q, J = 7 Hz, 2 each, OCH_2CH_3), 4.82 (br s, 1, CH–OH), 6.25 (q, J = 1 Hz, 1, CH=), 6.3 (s, 1, 5-H); MS m/e 282 (M^+).

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.44; H, 7.70; N, 9.85.

2,4-Diethoxy-6-(3-ethoxy-2-methylacryloyl)pyrimidine (9a). To pyrimidinecarbinol **8a** (270 mg, 0.96 mmol) in benzene (1.5 mL) and petroleum ether (1.5 mL) was added activated MnO_2[32] (448 mg, 5.2 mmol), and the mixture was stirred at room temperature for 24 h. Additional MnO_2 (200 mg, 2.3 mmol) was then added. After 72 h, the reaction mixture was filtered with the aid of benzene (2 × 20 mL), and the filtrate was concentrated in vacuo. The residual oil (249 mg) solidified on standing. This crude product (<10% carbinol on the basis of NMR data) was used without purification in subsequent reactions. Analytical material could be obtained by allowing the reaction to proceed entirely to the ketone, as followed by TLC (silica gel; $CHCl_3$/absolute EtOH, 9:1) and recrystallization of this product from petroleum ether. This sequence typically required additional MnO_2 and 6–7 days reaction time: mp 74–74.5 °C; NMR ($CDCl_3$) δ 1.36, 1.41, and 1.45 (t, 3 each, OCH_2CH_3), 1.87 (d, J = 1 Hz, 3, $=CCH_3$), 4.14, 4.46, and 4.50 (q, 2 each, OCH_2CH_3), 6.69 (s, 1, 5-H), 7.84 (q, J = 1 Hz, 1, CH=); MS m/e 280 (M^+).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.70; H, 6.99; N, 9.95.

6-(2-Amino-5-methylpyrimidin-4-yl)-2,4-diethoxypyrimidine (10a). The crude pyrimidinyl ketone **9a** (220 mg) mixed with guanidine carbonate (149 mg, 1.24 mmol) in 10 mL of absolute ethanol was heated at reflux for 16 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to leave a light brown solid. Petroleum ether (20 mL) was added and decanted off after stirring for 5 min. The solid residue was then extracted, i.e., stirred and decanted, with anhydrous ethyl ether (2 × 20 mL), followed by chloroform (2 × 20 mL). Evaporation of the ether layer in vacuo yielded 127 mg of analytically pure white product. Evaporation of the chloroform extracts in vacuo yielded 13 mg of additional product (total yield 65%): mp 110–111 °C; UV λ_{max} (H_2O, pH 0.9) 325 nm (ϵ 5610), 292 sh (4900); (pH 8.9) 313 (5170), 271 (5140); NMR ($CDCl_3$) δ 1.42 and 1.46 (t, 3 each, OCH_2CH_3), 2.42 (s, 3, 5′-CH_3), 4.52 and 4.55 (q, 2 each, OCH_2CH_3), 5.35 (br s, 2, NH_2), 7.02 (s, 1, 5-H), 8.34 (s, 1, 6′-H); MS m/e 275 (M^+).

Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.43; H, 6.45; N, 25.17.

6-(2-Aminopyrimidin-4-yl)-2,4-diethoxypyrimidine (10c). The generation of 2,4-diethoxy-6-lithiopyrimidine from 6-bromo-2,4-diethoxypyrimidine (**6b**,[27] 2.0 g, 8.1 mmol) and n-butyllithium (3.5 mL of a 2.4 M solution in hexane, 8.4 mmol) in THF (50 mL) was accomplished in the manner previously described for **8a**. After the addition of β-benzyloxyacrolein **7b**[30,31] (1.4 g, 8.9 mmol) in THF (5 mL), the reaction solution was stirred and quenched as described for **8a**. The concentration of the $MgSO_4$-dried ether layers left a red oil which was subsequently oxidized with activated MnO_2 (1.5 g, 17 mmol) in 5 mL of petroleum ether/benzene (2:1). When no further oxidation was indicated by TLC (benzene/EtOAc, 4:1; I_2 visualization), the mixture was filtered with additional benzene, and the filtrate was concentrated in vacuo. The residual oil was mixed with guanidine carbonate (2.0 g, 16.7 mmol) in absolute ethanol (30 mL), and the mixture was heated at reflux for 16 h. After filtration and concentration in vacuo of the reaction mixture, the residual brown oil was extracted with anhydrous ethyl ether (2 × 100 mL). Concentration of the ether layers produced a brown residue which was subsequently extracted with petroleum ether (3 × 150 mL). On reduction of the volume of the petroleum ether extracts to 10 mL, **10c** (274 mg, 13% yield) precipitated from solution. Analytical material was obtained by recrystallization from ethyl ether/$CHCl_3$, following a decolorizing charcoal treatment: mp 137–138 °C; UV λ_{max} (H_2O, pH 0.9) 330 nm sh (ϵ 7130), 314 (7680), 302 sh (6850); (pH 9.1) 303 (6950); NMR ($CDCl_3$) δ 1.40 and 1.46 (t, 3 each, OCH_2CH_3), 4.43 and 4.47 (d, 2 each, OCH_2CH_3), 5.2 (s, 2, NH_2), 7.29 (s, 1, 5-H), 7.57 (d, J = 5 Hz, 1, 5′-H), 8.42 (d, J = 5 Hz, 1, 6′-H); MS m/e 261 (M^+).

Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.81. Found: C, 55.45; H, 5.49; N, 26.60.

6-(2-Aminopyrimidin-4-yl)-2,4-diethoxy-5-methylpyrimidine (10b). The generation of 2,4-diethoxy-6-lithio-5-methylpyrimidine from **6b** (522 mg, 2.0 mmol) and n-butyllithium (0.8 mL of a 2.4 M solution in hexane, 2.2 mmol) in THF (15 mL) was accomplished as previously described. A solution of β-benzyloxyacrolein (**7b**, 350 mg, 2.16 mmol) in THF (5 mL) was added, and the resultant reaction mixture was stirred at <−80 °C for 1.25 h. After being warmed to 0 °C over 30 min, the reaction solution was inversely quenched with a mixture of ethyl ether (50 mL) and a 20% aqueous NH_4Cl solution (50 mL). Following the extraction of the aqueous layer with additional ethyl ether (2 × 40 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to an oil. This oil was oxidized in the manner described for **10c**. On dissolution of the oxidation products in absolute ethanol (20 mL) and addition of guanidine carbonate (450 mg, 3.75 mmol), the reaction mixture was heated at reflux for 12 h. The treatment of these reaction products in a manner analogous to the procedure described for **10c** provided, on reduction of the volume of petroleum ether extracts to 10 mL, **10b** (136 mg, 25% yield). After treatment with decolorizing charcoal, recrystallization from $CHCl_3$/ethyl ether provided analytical material: mp 142.5–143.5 °C; UV λ_{max} (H_2O, pH 0.9) 312 nm (ϵ 7420), 278 sh (5040); (pH 8.9) 300 (6890), 278 sh (5950); NMR ($CDCl_3$) δ 1.40 (t, 6, OCH_2CH_3), 2.22 (s, 3, 5-CH_3), 4.40 and 4.47 (q, 2 each, OCH_2CH_3), 5.26 (br s, 2, NH_2), 7.06 (d, J = 5 Hz, 1, 5′-H), 8.41 (d, J = 5 Hz, 1, 6′-H); MS m/e 275 (M^+).

Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.64; H, 6.32; N, 25.21.

6-(2-Amino-5-methylpyrimidin-4-yl)-2,4-diethoxy-5-methylpyrimidine (10d). The 6-lithio derivative was prepared from **6b** (1.044 g, 4 mmol) and n-butyllithium (1.8 mL of a 2.4 M solution in hexane, 4.32 mmol) in THF (20 mL) as previously described. Following the addition of β-ethoxy-α-methylacrolein (**7a**, 479 mg, 4.2 mmol) in THF (5 mL), the reaction mixture was stirred at <−80 °C for 1.5 h, with gradual warming to 0 °C allowed over the next 40 min. The reaction solution was quenched, worked up, and oxidized in the manner of **10c**. After filtration and concentration of the oxidation products, the residual oil was dissolved in absolute ethanol (15 mL).

On the addition of guanidine carbonate (1.0 g, 8.33 mmol), the mixture was heated at reflux for 18 h. Following a filtration with the aid of absolute ethanol (20 mL), the filtrate was concentrated in vacuo to a solid residue. The extraction of this residue with anhydrous ethyl ether (3 × 10 mL) and the subsequent concentration of the ether layer provided a lighter colored solid. Extraction of this solid with petroleum ether (4 × 5 mL) yielded white solid **10d** (285 mg, 25% yield) after partial concentration of the solvent. Analytical material was obtained by vacuum sublimation (6 mmHg, 155 °C): mp 152–153 °C; UV λ_{max} (H_2O, pH 0.9) 320 nm (ϵ 5150), 264 (5820); (pH 9.24) 305 (5190), 272 (6370); NMR ($CDCl_3$) δ 1.38 and 1.41 (t, 3 each, OCH_2CH_3), 1.91 and 2.0 (s, 3 each, Ar–CH_3), 4.35 and 4.47 (q, 2 each, OCH_2CH_3), 5.02 (br s, 2, NH_2), 8.23 (s, 1, 6′-H); MS *m/e* 289 (M^+).

Anal. Calcd for $C_{14}H_{19}N_5O_2$: C, 58.11; H, 6.62; N, 24.21. Found: C, 58.26; H, 6.45; N, 24.37.

2,4-Diethoxy-6-(2-hydroxy-5-methylpyrimidin-4-yl)pyrimidine (11a). To the ice-cooled bipyrimidine **10a** (360 mg, 1.31 mmol) was added 1 mL of H_2O, 1 mL of 6 M HCl, and 0.5 mL of concentrated H_2SO_4. Over a period of 10 min a solution of sodium nitrite (360 mg, 5.22 mmol) in H_2O (1 mL) was dripped in, and gas evolution was evident. The reaction was stirred at 25 °C for 3.5 h, after which time 20 mL of H_2O was added, and the mixture was extracted with chloroform (2 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated in vacuo to yield a yellow solid. The solid was transferred to a sintered glass funnel with 25 mL of petroleum ether and then washed with 5 mL of benzene to give the product (139 mg, 39% yield). An analytical sample was obtained by crystallization from petroleum ether/benzene: mp 162–163 °C; UV λ_{max} (H_2O, pH 1.0) 336 nm (ϵ 6570), 276 (4180); (pH 8.9) 321 (6420), 272 sh (3970); (pH 13.0) 316 (5810), 268 (5420); NMR ($CDCl_3$) δ 1.42 and 1.46 (t, 3 each, OCH_2CH_3), 2.37 (s, 3, 5′-CH_3), 4.51 and 4.53 (q, 2 each, OCH_2CH_3), 7.00 (s, 1, 5-H), 8.0–8.8 (br s, 1, OH), 8.22 (s, 1, 6′-H); MS *m/e* 276 (M^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.49; H, 5.84; N, 20.17.

2,4-Diethoxy-6-(2-hydroxypyrimidin-4-yl)pyrimidine (11c). To ice-cooled **10c** (75 mg, 0.29 mmol) was added 1 mL of H_2O, 0.3 mL of 6 N HCl, and 0.15 mL of concentrated H_2SO_4. Over a period of 10 min a solution of sodium nitrite (80 mg, 1.16 mmol) in H_2O (0.5 mL) was dripped in, and the reaction mixture was stirred for 1.5 h. After dilution with 20 mL of H_2O, an extraction with $CHCl_3$ (2 × 20 mL) was performed, and the resultant organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to a white solid. Washing with petroleum ether/benzene (5:1, 2 × 10 mL) provided nearly pure **11c** (53.4 mg, 71% yield). Analytical material was obtained by recrystallization from benzene/$CHCl_3$, after treatment with decolorizing charcoal: mp 223–223.5 °C; UV λ_{max} (H_2O, pH 0.9) 333 nm (ϵ 7000), 305 sh (7000). 293 (7200); (pH 8.9) 317 (8700); (pH 13) 318 (6600), 299 (6600); NMR ($CDCl_3$) δ 1.40 and 1.46 (t, 3 each, OCH_2CH_3), 4.47 and 4.49 (q, 2 each, OCH_2CH_3), 7.41 (s, 1, 5-H), 7.47 (d, J = 6 Hz, 1, 5′-H), 8.13 (d, J = 6 Hz, 1, 6′-H); MS *m/e* 262 (M^+).

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.95; H, 5.38; N, 21.37. Found: C, 54.70; H, 5.25; N, 21.39.

2,4-Diethoxy-6-(2-hydroxypyrimidin-4-yl)-5-methylpyrimidine (11b). The diazotization–hydrolysis of **10b** was carried out essentially according to the directions for **11c**. The resulting solid (~200 mg) was washed with petroleum ether/benzene (5:1, 2 × 5 mL) and 2 mL of anhydrous ethyl ether to afford **11b** in 60% yield. Dissolution of this sample in hot benzene, treatment with decolorizing charcoal, filtration, and concentration gave analytically pure material: mp 181–182.5 °C; UV λ_{max} (H_2O, pH 0.9) 306 nm (ϵ 7700); (pH 8.8) 310 (8600), (pH 12.9) 300 (8030), 275 (6600); NMR ($CDCl_3$) δ 1.43 (t, 6, OCH_2CH_3), 2.37 (s, 3, 5-CH_3), 4.42 and 4.48 (q, 2 each, OCH_2CH_3), 7.04 (d, J = 5 Hz, 1, 5′-H), 8.16 (d, J = 5 Hz, 1, 6′-H), 9.9 (br s, 1, NH); MS *m/e* 276 (M^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.48; H, 5.87; N, 19.99.

2,4-Diethoxy-6-(2-hydroxy-5-methylpyrimidin-4-yl)-5-methylpyrimidine (11d). The diazotization–hydrolysis of sublimed **10d** was done in the manner of **11c** and, on similar workup, provided solid **11d** (150 mg, 70% yield). Analytical material was obtained by washing the product with petroleum ether (2 × 25 mL) and benzene (25 mL): mp 190.5–191.5 °C; UV λ_{max} (H_2O, pH 0.9) 326 nm (ϵ 6430), 267 (6830); (pH 8.9) 314 (6690), 268 (5180); (pH 12.6) 308 (6740), 270 (7180); NMR ($CDCl_3$) δ 1.37 and 1.41 (t, 3 each, OCH_2CH_3), 1.99 (s, 6, 5- and 5′-CH_3), 4.33 and 4.45 (q, 2 each, OCH_2CH_3), 7.99 (s, 1, 6′-H); MS *m/e* 290 (M^+).

Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 57.78; H, 5.98; N, 19.58.

6-(2-Hydroxy-5-methylpyrimidin-4-yl)uracil (4). A solution of **11a** (232 mg, 0.84 mmol) in 6 N HCl (30 mL) was heated at reflux for 1 h. Removal of the solvent in vacuo left a residue which, on crystallization from H_2O after a decolorizing charcoal treatment, yielded analytically pure **4**: 126 mg, 68% yield; 224–226 °C dec; UV λ_{max} (H_2O, pH 0.9) 320 nm (ϵ 6840); (pH 7.2) 319 (6980); (pH 12.9) 299 (9760); NMR [$(CD_3)_2SO$] δ 2.06 (s, 3, CH_3), 5.58 (s, 1, 5-H), 8.12 (s, 1, 6′-H); MS *m/e* 220 (M^+).

Anal. Calcd for $C_9H_8N_4O_3 \cdot 0.25H_2O$: C, 48.10; H, 3.81; N, 24.93. Found: C, 48.05; H, 3.91; N, 25.00.

6-(2-Hydroxypyrimidin-4-yl)thymine (1). A solution of **11b** (170 mg, 0.62 mmol) in 6 N HCl (15 mL) was heated at reflux for a period of 1.5 h. After removal of the solvent in vacuo, the residual solid was washed with $CHCl_3$ to afford **1** (76 mg, 56% yield). Analytical material was obtained by recrystallization from H_2O, following treatment with decolorizing charcoal: 273–275 °C dec; UV λ_{max} (H_2O, pH 0.9) 317 nm (ϵ 8980); (pH 7.2) 314 (8740); (pH 12.9) 303 (11 100); NMR [$(CD_3)_2SO$] δ 1.77 (s, 3, CH_3), 6.58 (d, J = 6 Hz, 1, 5′-H), 8.18 (d, J = 6 Hz, 1, 6′-H); MS *m/e* 220 (M^+).

Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 48.83; H, 3.56; N, 25.43.

6-(2-Hydroxypyrimidin-4-yl)uracil (2). A solution of **11c** (77 mg, 0.29 mmol) in 6 N HCl (10 mL) was heated at reflux for 1.5 h. Removal of the solvent in vacuo left solid **2** (50 mg, 84% yield). An analytical sample was obtained by recrystallization from H_2O, following a treatment with decolorizing charcoal: 242–243 °C dec; UV λ_{max} (H_2O, pH 0.9) 336 nm sh (ϵ 6970), 314 (9160), 303 (9360); (pH 7.2) 336 sh (6730), 314 (8300), 304 (8480); (pH 12.9) 325 (11 250); NMR [$(CD_3)_2SO$] δ 6.39 (s, 1, 5-H), 7.03 (d, J = 6 Hz, 1, 5′-H), 8.17 (d, J = 6 Hz, 1, 6′-H); MS *m/e* 206 (M^+).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.60; H, 2.93; N, 27.18. Found: C, 46.38; H, 2.82; N, 26.96.

6-(2-Hydroxy-5-methylpyrimidin-4-yl)thymine (3). A solution of **11d** (100 mg, 0.34 mmol) in 6 N HCl (10 mL) was heated at reflux for a period of 2 h. After concentration of the reaction solution to an oil, $CHCl_3$ (5 mL) was added, and the flask was left uncovered overnight. Evaporation of the solvent during the night left a solid yellow crystalline material, which was washed with 5 mL of anhydrous ether/absolute ethanol (4:1) to leave **3** (70 mg, 87% yield). Recrystallization from absolute ethanol provided analytical **3** as a white fluffy powder: 310–312 °C dec; UV λ_{max} (H_2O, pH 0.9) 322 nm (ϵ 7050), 255 (6500); (pH 7.2) 318 (7090), 258 (6250); (pH 12.9) 302 (12 970); NMR [$(CD_3)_2SO$] δ 1.57 and 1.93 (s, 3 each, CH_3), 8.14 (s, 1, 6′-H); MS *m/e* 234 (M^+).

Anal. Calcd for $C_{10}H_{10}N_4O_3 \cdot 0.25H_2O$: C, 50.31; H, 4.43; N, 23.47. Found: C, 50.35; H, 4.30; N, 23.58.

Acknowledgment. J.D.B. has held a Lilly Fellowship in Chemistry. This work has been supported by the National Science Foundation Research Grant CHE 76-23543.

Registry No.—**5b,** 64188-81-4; **6a,** 64188-82-5; **6b,** 64188-83-6; **7a,** 42588-57-8; **7b,** 4652-40-8; **8a,** 64188-84-7; **9a,** 64188-85-8; phosphorus oxybromide, 7789-59-5; 5-methylbarbituric acid, 2417-22-3; guanidine carbonate, 124-46-9.

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Notes

Rearrangement of Cinnamyl Groups from O^6 to C-8 in the Guanine Series

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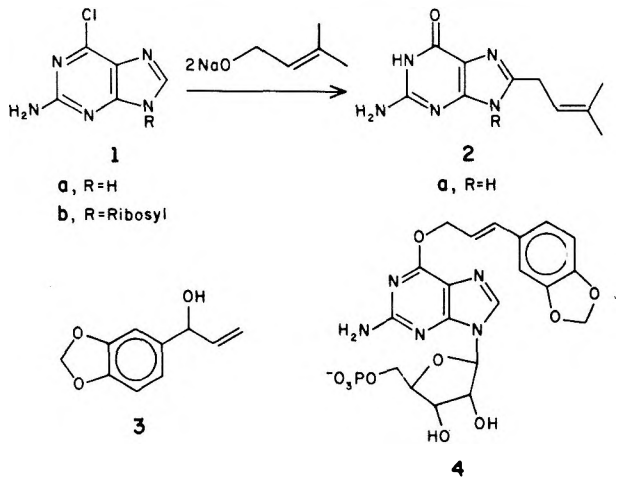
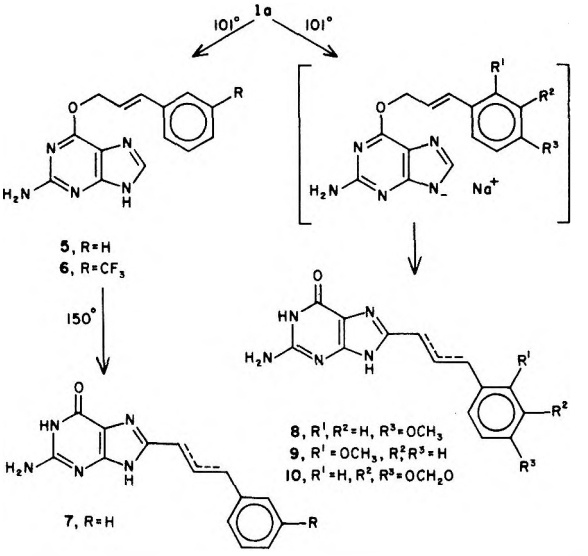
Received August 2, 1977

It was established in this Laboratory that displacement reactions of 2-amino-6-chloropurine (**1a**) with the sodium salts of allylic alcohols proceed through an O^6 ether to yield 8-substituted guanines (e.g., **2a**),[2] with the following stipulations: (a) the O^6 to C-8 rearrangement occurs with overall allylic retention and is partially controlled by the degree of methyl substitution of the allylic group and by the temperature, (b) the rearrangement proceeds with greatest facility through anionic species, and (c) it occurs intramolecularly and most logically by two [3,3]sigmatropic shifts via C-5.



Derivatives of allylbenzene and propenylbenzene are widely occurring plant constituents, and many which are present as major components of common spices and flavorings exhibit biological activity.[3] It has been shown that allylbenzene derivatives can be oxidized metabolically to give allylic alcohols.[4,5] More specifically, safrole (3,4-methylenedioxyallylbenzene), which is a hepatotoxin and a hepatocarcinogen, is oxidized in the liver, inter alia, to 1-(3,4-methylenedioxyphenyl)-2-propen-1-ol (**3**), a more potent carcinogen than the parent safrole.[5] Furthermore, a University of Wisconsin group has shown that the synthetic acetate of **3**, as a model for metabolic activation, reacts with guanosine monophosphate to give the O^6-allylic ether **4**. These reports led us to investigate the rearrangement of O^6-cinnamyl ethers of guanine.

Treatment of 2-amino-6-chloropurine (**1a**) with the sodium salt of either cinnamyl alcohol or *m*-trifluoromethylcinnamyl alcohol in refluxing dioxane (101 °C) for 4 h gave the corresponding O^6 ether **5** or **6**, respectively, of guanine. At 101 °C, no rearrangement product was detectable by thin-layer chromatography, even after heating at reflux for 24 h. However, when O^6-cinnamylguanine (**5**) was converted to its sodium salt with 1 equiv of sodium hydride and heated at 150 °C for 24 h in either anhydrous diglyme or dimethylformamide, rearrangement occurred to a mixture of 8-(3-phenyl-1-propenyl)guanine and 8-(3-phenyl-2-propenyl)guanine (**7**). When the *m*-trifluoromethyl compound **6** was treated under the same conditions at 150 °C, guanine was the only purine product that could be detected.



Electron-donating groups on the phenyl ring facilitated rearrangement. Thus, treatment of **1a** separately with the sodium salts of *p*-methoxycinnamyl alcohol,[6] o-methoxycinnamyl alcohol,[6] and 3-(3,4-methylenedioxyphenyl)-2-propen-1-ol[5] in refluxing dioxane (101 °C) gave the corresponding C-8 substituted guanines **8–10**. The product in each case was isolated as an approximately 1:1 mixture of the double-bond isomers. TLC analysis of the progress of the re-

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action showed that the O^6 ether was formed initially and was converted slowly to the C-8 product (**8–10**). At the end of 24 h, no detectable O^6 intermediate remained in the reaction mixture. Assignment of the structure of each C-8 product was based on the absence of an 8-H signal in the NMR and on the upfield shift of the signal for the methylene hydrogens from $\delta \sim 5$ for O^6 substitution to δ 3.4–3.7 for C substitution.

We had noted earlier that γ-methyl substitution on the migrating allylic group facilitates O^6 to C-8 rearrangement.[2] The present results support the hypothesis that γ substituents influence the ease of rearrangement through an electronic rather than a steric factor since there is little difference in bulk between the substituted phenyl rings. On a qualitative basis, these results are similar to those for the ortho Claisen rearrangement of substituted cinnamyl *p*-tolyl ethers, which have a negative ρ and can be correlated to σ^+.[7]

In order to evaluate the possible biological significance of the O^6 to C-8 rearrangement, we extended our investigations to guanosine derivatives. Since O^6-(3-methyl-2-butenyl)-guanine [O^6-(Δ^2-isopentenyl)guanine] rearranges more readily than any other allylic ether tried, we examined the stability of the related O^6-(3-methyl-2-butenyl)guanosine as a control for the effect of 9-ribosyl substitution. Treatment of 2-amino-6-chloro-9-(β-D-ribofuranosyl)purine (**1b**) with sodium 3-methyl-2-butene 1-oxide in 3-methyl-2-buten-1-ol at 115 °C in 5 min gave the corresponding O^6 ether as the sole product. In a typical experiment, O^6-(3-methyl-2-butenyl)-guanosine was treated with 1 equiv of sodium hydride in anhydrous dimethylformamide at 100 °C for 12 h. Hydrolytic removal of the ribose in 1 M HCl and high-performance liquid chromatography of the products failed to show the presence of any detectable amount of 8-(3-methyl-2-butenyl)guanine by comparison of retention time with that of an authentic sample. Similar results were obtained using up to 4 equiv of sodium hydride and raising the temperature to 170 °C.

We have shown that O^6-cinnamyl ethers of guanine can rearrange to C-8 substituted guanines and that this rearrangement is greatly facilitated by electron-donating substituents in the phenyl ring. We did not detect the parallel O^6 to C-8 rearrangement of allylic guanosine derivatives, presumably because the ribosidated nucleus is unable to form an anion. Thus, the event of in vivo O^6-cinnamylation of a guanosine or guanylic unit cannot be excluded as a *sufficient* basis for the observed biological effect, e.g., in the case of safrole.[5] O^6-Alkylation in a DNA template has already been implicated in miscoding operations.[8,9] Were N-7 the alternative site[9] of mutational cinnamylation, the formation of such 7-substituted guanosine units would have to be sufficient to cause deletion or to effect miscoding. The possibility of a subsequent N-7 to C-8 [3,2]sigmatropic shift remains in chemical consideration for 7-allylated guanosines, even though 7-allylated guanines are stable,[2b,10] and these should be explored as special cases of 7-alkylated guanosines.

Experimental Section

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on Varian Associates A-60, EM-390, or HA-100 spectrometers using tetramethylsilane as an internal standard. The ultraviolet spectra were obtained on a Beckman Acta Model M VI spectrometer. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for quantitative electronic absorption spectra. Low-resolution mass spectra were obtained on a Varian MAT CH-5 spectrometer. Field desorption and high-resolution mass spectra were obtained on a Varian MAT 731 spectrometer, coupled with a 620i computer and STATOS recorder.

***O*^{6}-Cinnamylguanine (5).** A suspension of sodium hydride (283 mg of a 50% oil dispersion, 5.90 mmol), dry dioxane (24 mL), and cinnamyl alcohol (791 mg, 5.90 mmol) was stirred under a nitrogen atmosphere. After evolution of hydrogen had ceased, 2-amino-6-chloropurine (**1a**, 500 mg, 2.95 mmol) was added, and the mixture was heated at reflux for 4 h. The solvent was removed in vacuo. The residue was dissolved in water (10 mL) and washed with ether (2 × 10 mL). The water layer was acidified to pH 6 with 20% aqueous acetic acid. After cooling, the solid was removed by filtration. Recrystallization from ethanol gave 440 mg (56%) of tan solid mp 165–175 °C dec; λ_{max} (0.1 M HCl, EtOH) 281 nm sh (ϵ 10 670), 274 (10 880), 239 (21 760); (EtOH) 282 sh (8530), 272 (11 310), 266 sh (10 990), 236.5 (24 660); (0.1 M NaOH, EtOH) 281 sh (9810), 273 (10 990), 266 sh (10 240), 236.5 (21 420); NMR [$(CD_3)_2SO$] δ 5.16 (d, 2, CH_2), 6.22 (br, 2, NH_2), 6.62–7.05 (m, 2, CH=CH), 7.34 (m, 5, C_6H_5) 7.89 (s, 1, pu-H); field desorption mass spectrum, *m/e* 267 (M^+).

Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.98; H, 4.90; N, 26.04.

***O*^{6}-(*m*-Trifluoromethylcinnamyl)guanine (6).** A suspension of sodium hydride (247 mg of a 50% oil dispersion, 5.15 mmol), dry dioxane (25 mL), and *m*-trifluoromethylcinnamyl alcohol (1.04 g, 5.15 mmol) was stirred under a nitrogen atmosphere for 6 h at 25 °C. To this mixture 2-amino-6-chloropurine (**1a**) was added, and the mixture was heated at reflux for 4 h. After cooling, glacial acetic acid (0.3 mL) was added, and the solid material was removed by filtration. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate (1 mL). The ethyl acetate solution was applied to an 8-g silica gel column. Elution with ethyl acetate gave a fraction containing 606 mg (72%) of light yellow solid: mp 75–80 °C; λ_{max} (0.1 M HCl, EtOH) 294 nm sh (ϵ 9700), 285 (11 030), 246 (19 500); (EtOH) 282 (10 360), 244.5 (22 590); (0.1 M NaOH, EtOH) 283 (9820), 247 (18 390), 227 (14 660); NMR [$(CD_3)_2SO$] δ 5.10 (s, 2, CH_2), 6.19 (br, 2, NH_2), 6.4–7.0 (m, 2, CH=CH), 7.3–7.88 (m, 4, $C_6H_4CF_3$), 7.81 (s, 1 H, pu-H); field desorption mass spectrum, *m/e* 335 (M^+).

Anal. Calcd for $C_{15}H_{12}F_3N_5O$: C, 53.68; H, 3.58; F, 17.00; N, 20.88. Found: C, 53.67; H, 3.50; F, 16.95; N, 20.65.

8-(3-Phenyl-1-propenyl)guanine and 8-(3-Phenyl-2-propenyl)guanine (7). A suspension of O^6-cinnamylguanine (**5**, 100 mg, 0.374 mmol) and sodium hydride (18 mg of a 50% oil dispersion, 0.374 mmol) in dry diglyme (3 mL) was stirred for 2 h at 25 °C. The mixture was heated at 150 °C for 24 h under a nitrogen atmosphere and was then treated with glacial acetic acid (0.3 mL) and ether (50 mL). The solid was filtered and washed with water (5 mL). Recrystallization from 50% aqueous ethanol gave 76 mg (76%) of light tan solid, mp >300 °C. NMR showed a mixture of the double-bond isomers [$(CD_3)_2SO$]: δ 3.48–3.65 (m, 2, CH_2), 6.1–6.85 (m, 4, CH=CH, NH_2), 7.1–7.5 (m, 5, C_6H_5); mass spectrum (10 eV), *m/e* 267 (M^+).

Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.68; H, 4.92; N, 25.98.

8-[3-(3,4-Methylenedioxyphenyl)-1-propenyl]guanine and 8-[3-(3,4-Methylenedioxyphenyl)-2-propenyl]guanine (10). A suspension of sodium hydride (283 mg of a 50% oil dispersion, 5.90 mmol), dry dioxane (50 mL), and 3-(3,4-methylenedioxyphenyl)-2-propen-1-ol (1.05 g, 5.90 mmol) was stirred at 25 °C under a nitrogen atmosphere. After evolution of hydrogen had ceased (~6 h), 2-amino-6-chloropurine (500 mg, 2.95 mmol) was added, and the mixture was heated at reflux for 24 h. After cooling, the dioxane was removed in vacuo, and ether (50 mL) was added to the residue. Glacial acetic acid (0.5 mL) was added to the mixture with vigorous stirring. The solid was removed by filtration and washed successively with ethanol, water, and ethanol to give 605 mg (66%) of light tan solid. An analytical sample was obtained by suspending 100 mg of the solid in refluxing ethanol and adding water until the solid dissolved. The hot solution was treated with charcoal and filtered through a Celite pad. The volume of the solution was then reduced to ~15 mL by boiling. After cooling, the solid was collected, mp 274–280 °C dec. NMR showed a mixture of the double-bond isomers [$(CD_3)_2SO$]: δ 3.4–3.6 (m, 2, CCH_2C), 5.98 (s, 2, OCH_2O), 6.1–6.74 (m, 4, CH=CH, NH_2), 6.75–7.05 (m, 3, C_6H_3); mass spectrum (10 eV), *m/e* 311 (M^+); high-resolution mass spectrum, *m/e* 311.1015 (calcd for $C_{15}H_{13}N_5O_3$).

Anal. Calcd for $C_{15}H_{13}N_5O_3$: C, 57.87; H, 4.21; N, 22.50. Found: C, 57.78; H, 4.32; N, 22.51.

A similar procedure was used to prepare mixtures of 8-[3-(*p*-methoxyphenyl)-1-propenyl]- and 8-[3-(*p*-methoxyphenyl)-2-propenyl]guanine (**13**) and of 8-[3-(*o*-methoxyphenyl)-1-propenyl]- and 8-[3-(*o*-methoxyphenyl)-2-propenyl]guanine (**14**). Satisfactory ^{1}H NMR spectra, low-resolution mass spectra, and high-resolution mass spectra were obtained.[11]

***O*^{6}-(3-Methyl-2-butenyl)guanosine** was prepared in a manner similar to other O^6-substituted guanosine derivatives:[12] mp 210–215 °C dec; field desorption mass spectrum, *m/e* 351 (M^+).

Acknowledgment. This work was supported by Research Grant CHE 76-23543 from the National Science Foundation. The high-resolution mass spectrometer and data processing

equipment were provided by Grants CA 11388 and GM 16864 from the National Institute of Health.

Registry No.—**1a**, 10310-21-1; **5**, 64189-11-3; **6**, 64189-12-4; **7** (2-propenyl isomer), 64189-13-5; **7** (1-propenyl isomer), 64189-14-6; **10** (1-propenyl isomer), 64189-15-7; **10** (2-propenyl isomer). 64189-16-8; cinnamyl alcohol, 104-54-1; *m*-trifluoromethylcinnamyl alcohol, 64189-17-9; 3-(3,4-methylenedioxyphenyl)-2-propen-1-ol, 17531-86-1; O^6-(3-methyl-2-butenyl)guanosine, 64189-18-0.

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Stereochemistry of the Furan–Maleic Anhydride Cycloaddition

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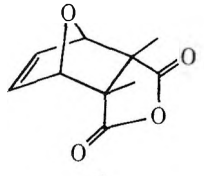
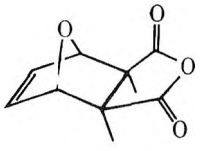
Received July 14, 1977

The crystalline product from the Diels–Alder reaction of furan (F) with maleic anhydride (M) was originally formulated as endo adduct **1**.[2] Woodward and Baer showed that the adduct actually has the exo configuration **2**.[3] Anet has stated[4]



1



2

that the exo isomer is initially formed about twice as fast as the endo isomer, and that the endo compound initially produced quickly disappears from the reaction mixture at room temperature.

The kinetically favored formation of the exo compound is a very unusual circumstance and constitutes the only known exception to the rule of predominant endo addition[5] in reactions where dienophiles and/or dienes are not heavily substituted.[6] We also find that all of the usual grounds for explaining endo selectivity (maximum accumulation of unsaturation,[7] secondary orbital interactions,[8] primary overlap at the reaction sites,[9] attractive dipole–dipole interactions, and dispersion forces[10]) are fulfilled in the furan–maleic anhydride cycloaddition. Consequently, we have reinvestigated this reaction using nuclear magnetic resonance spectroscopy.

In agreement with the previous work, the reaction of maleic anhydride with furan gives rise to the exo adduct **2**: mp 125–126 °C; NMR bands at δ 6.5 (2 H, multiplet), 5.3 (2 H, multiplet), 3.2 (2 H, singlet). In acetonitrile solution at 40 °C, initial concentrations of reactants both equal to 1.50 M, a small amount of *endo*-**1** is initially formed and identified by its NMR spectrum: δ 6.5 (multiplet), 5.4 (multiplet), 3.9 (multiplet). *However, the initial rate of formation of endo-***1** *is found to be larger than that for the formation of* **2**. At the end of 24 min the concentrations of **1** and **2** are the same, and the concentration of **2** exceeds that of **1** after that point. Endo adduct has essentially disappeared after 48 h, and the final concentration ratio of product to reactants is [*exo*-**2**]/[M] = 1.83 and K = [M][F]/[2] = 0.289 L mol^{-1}. Pure exo adduct decomposes to give only the addends. With the initial concentration of **2** equal to 0.120 M, the equilibrium concentration ratio is 0.348 and K = 0.256 L mol^{-1}.

At lower initial concentrations of reactants, the only initially discernable product is the endo adduct. With [M_0] = [F_0] = 0.50 M, 8% of the reactants are converted to **1** after 310 s, and the concentration of **1** slowly decreases after that time. Exo adduct **2** is only evident in the reaction mixture after 3000 s of reaction time. Several repetitions of all of these experiments gave congruent results.

Using the differential rate expressions directly[11] we find that our data yield the rate constants shown. The rate constant for formation of the endo adduct is actually almost 500 times larger than the exo adduct formation rate constant. Assuming comparable entropies of activation, this rate constant difference corresponds to an activation energy difference of 3.8 kcal favoring the endo adduct. The exo adduct is, however, 1.9 kcal/mol more stable than the endo adduct. Since the formations of both adducts are reversible, the exo adduct is eventually the final isolated product.

$$\mathrm{M} + \mathrm{F} \underset{4.37 \times 10^{-2}\ \mathrm{s}^{-1}}{\overset{7.29 \times 10^{-3}\ \mathrm{L\ m^{-1}\ s^{-1}}}{\rightleftharpoons}} \textit{endo}\text{-}\mathbf{1}$$

$$\mathrm{M} + \mathrm{F} \underset{4.40 \times 10^{-6}\ \mathrm{s}^{-1}}{\overset{1.60 \times 10^{-5}\ \mathrm{L\ m^{-1}\ s^{-1}}}{\rightleftharpoons}} \textit{exo}\text{-}\mathbf{2}$$

With these results, the furan–maleic anhydride reaction can be placed within the typical kinetic and thermodynamic pattern for Diels–Alder reactions.[5,12]

Acknowledgment. The financial support of the Robert A. Welch Foundation is greatly appreciated.

Registry No.—**1**, 64113-63-9; **2**, 64161-68-8; maleic anhydride, 108-31-6; furan, 110-00-9.

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0022-3263/78/1943-0518$01.00/0

Lewis Acid Rearrangement of 2,3-Epoxycarane. Formation of a Novel *m*-Menthenone

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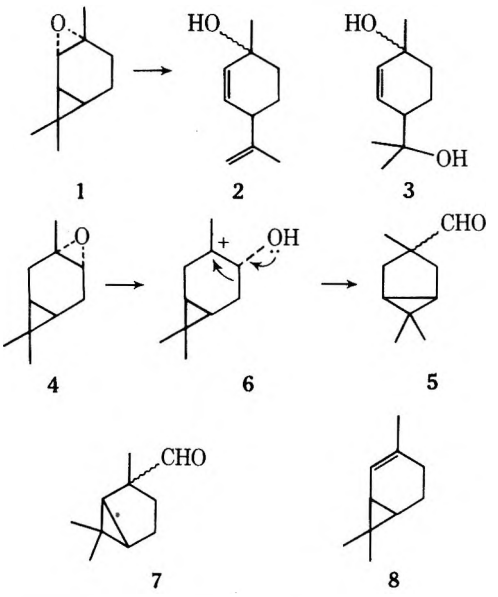
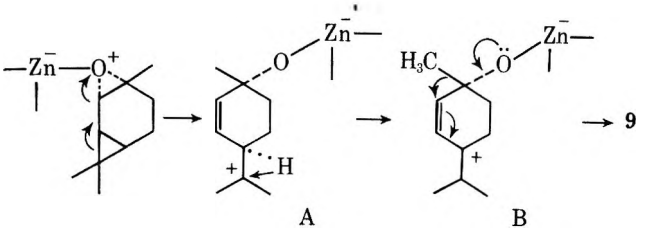
Rearrangement of 2,3-epoxycarane (**1**) employing metatitanic acid has been previously studied[1] and found to yield predominately alcohol **2**. It has also been reported[2] that epoxidation of 2,3-carene with peracetic acid leads directly, after saponification of acetates, to **2** and diol **3**. Recent work,[3]



consistent with earlier results, has shown that epoxide **1** undergoes rearrangement to **2** and a series of allylic alcohols and hydrocarbons derived most likely from **2**. This latter work employed a wide range of solid acids and bases SiO_2–Al_2O_3, Al_2O_3, $FeSO_4$, TiO_2–ZrO_2, and CAO, and in no case were carbonyl and/or ring-contraction products identified. Conversely, it has been found that 3,4-epoxycarane (**4**), using the above solid catalysts[3] and also zinc bromide ($ZnBr_2$),[4] gave relatively good yields of the ring-contraction product aldehyde **5** along with ketones and allylic alcohols, almost all of which could be derived from an intermediate of type **6**.

We had a need for aldehyde **7** which, in principle, could be formed from epoxide **1** by an analogous route using the strong

Scheme I



Lewis acid $ZnBr_2$. Accordingly, epoxide **1** was prepared essentially quantitatively from 2,3-carene (**8**) using *m*-chloroperbenzoic acid in a two-phase system reported[5] to be useful for very labile epoxide preparation. The NMR of **1** compared well to a published spectrum.[6] A conventional procedure using monoperphthalic acid gave considerable rearrangement to **2** and **3**.

Only a very small amount of an aldehyde was produced (see Table I). The aldehyde had a MS almost identical to **5**, which as previously discussed is formed from 3,4-epoxycarane (**4**). The yield could not be increased and not enough material could be isolated to determine if the aldehyde was the desired compound **7** or the known **5**. It is almost certain that the aldehyde in question is **5** derived from 3,4-epoxycarane (**4**), present as an approximately 2% impurity in the starting epoxide. *cis*-3-Caranone (**11**), the major product of $ZnBr_2$ rearrangement of **4**, was also detected. Production of **7** would require epoxide opening without cyclopropyl participation, which apparently does not occur to any detectable extent. Rearrangement of **1** employing stannic chloride ($SnCl_4$) led to lower yields of ketone; results are included in Table I along with the products of the $ZnBr_2$ rearrangement in benzene.

Treatment of epoxide **1** with $ZnBr_2$ in refluxing toluene yielded a number of terpene hydrocarbons. The reaction products and amounts are given in Table I and are listed as they elute from the VPC. α-Terpinene, limonene, and β-phellandrene are reported for the first time as products of acid rearrangement of 2,3-epoxycarane (**1**). Of considerably more interest was the major product, a *m*-menthenone, shown to be 2-methyl-4-isopropylcyclohex-3-en-1-one (**9**) amounting to 40% of the volatile products. The IR of **9** showed it to contain a nonconjugated carbonyl (ν = 1720 cm^{-1}). The 100-MHZ NMR spectrum was in accord with **9** and exhibited a sharp six-proton doublet at δ 1.04 (J = 7 Hz; CH_3, 1 and 2), a three-proton doublet at 1.14 (J = 7 Hz, CH_3, 3), a one-proton quintet centered at 2.3 (J = 7 Hz, H_a), a four-proton narrow multiplet at 2.46 (H_b), a broad one-proton quartet with additional splitting at 2.88 (J = 7 Hz, H_c), and a one-proton doublet with additional splitting at 5.37 (J = 3 Hz, H_d). Proton

Table I. 2,3-Epoxycarane Rearrangement Products

Compound	Registry no.	Structure determined by	Area, %[a] b	c	d
α-Terpinene	99-86-5	MS	0.1	0.4	0.4
Limonene	138-86-3	MS	1.9	0.4	1.1
A *p*-menthatriene—possibly 1,4,8-*p*-menthatriene	28233-65-0	MS	0.2	0.4	<0.1
β-Phellandrene and a *p*-menthatriene	555-10-2	MS	0.6	0.4	<0.1
p-Cymene	99-87-6	IR, MS	17.0	17.0	24.2
Terpinolene	586-62-9	IR, MS	6.0	0.5	0.1
Aldehyde (probably aldehyde **5**)	13124-67-9	MS	0.7	<0.1	<0.1
p-α-Dimethylstyrene	1195-32-0	IR, NMR, MS	7.7	22.7	<0.5
2-Methyl-4-isopropylcyclohex-3-en-1-one (**9**)	63028-18-2	See Exptl Sect	40.4	29.1	17.1
% total volatiles identified			74.4	70.9	43.4

[a] VPC peak area as a percent of total peak area. [b] $ZnBr_2$–refluxing toluene. [c] $ZnBr_2$–refluxing benzene. [d] ≃2% $SiCl_4$ in benzene cooled in ice bath.

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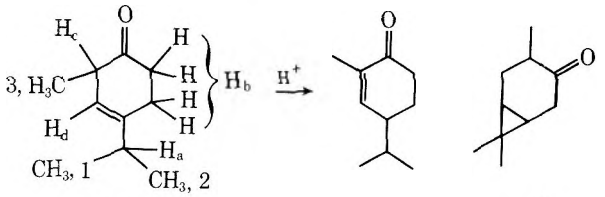
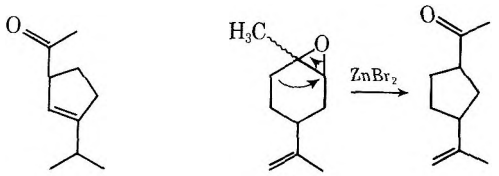


9 10 11

H_a exhibited five lines of the theoretical septet due to the very low intensity of outer septet lines and low S/N ratio encountered in microcell techniques. Structure **9** was further confirmed by isomerization with *p*-toluenesulfonic acid to the known ketone **10**.[7]

Formation of the major product, ketone **9**, can be postulated by a mechanism outlined in Scheme I. Anti-Markovnikov opening of the epoxide ring with cyclopropyl participation could yield carbonium ion A. In the previous studies,[1-3] this ion could account for the reported products without carbon rearrangement. However, by employing conventional Lewis acids ($ZnBr_2$ and $SiCl_4$), it appears that a fundamental rearrangement involving both a hydride and methyl shift takes place (A → B → **9**). The stereochemistry of the oxide and resulting carbonium ions is most likely as shown, since the stereochemistry of the starting oxide, prepared with peracid, has been shown to be *trans*-**1**.[6]

The methyl ketone **12**, which could be formed from ion B by ring migration, was not detected in the reaction mixture. In contrast, a mixture of *cis*- and *trans*-limonene oxide (**13**) was found[8] to undergo rearrangement without methyl migration but with ring contraction (**13** → **14**).[9] Models show that



12 13 14

these results can be explained by stereochemical differences, since the axial methyl group is ideally disposed for migration (axial and parallel to the p orbitals of the double bond) in intermediates (A, B) leading to ketone **9**.

For limonene oxide (**13**), both the methyl group and ring carbon are equally disposed stereochemically to migration. If it is assumed that the transition state resembles the ground state, then the group with the highest migratory aptitude (the secondary ring carbon) will undergo rearrangement.

Experimental Section

Analyses by VPC were performed on a Perkin-Elmer 900 equipped with dual 12 ft, ⅛ in. i.d. glass columns, modified for on-column injection and packed with 5% Triton X-305 on Chromosorb W. H.P. 80–100 mesh. The oven temperature was programmed from 70 to 170 °C at 2 °C/min. A flow rate of 35 mL/min of helium was employed. Compounds were purified as clear liquids by collection in glass capillaries or ⅛-in. glass tubing from an F&M 810 GC equipped with a TC detector, ¼-in. glass column, and generally operated as above. IR spectra were determined using a PE-221 or PE-281; MS were determined using a Hitachi-RMU-6L. NMR were determined on a Varian T-60-A or JEOL-MH-100 in $DCCl_3$ using Me_4Si as an internal standard. Microanalysis was performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

2,3-Epoxycarane (1). *m*-Chloroperbenzoic acid (1.28 g, 6.3 mmol) was added over 1.5 h to a mixture of 0.75 g (5.5 mmol) of 2,3-carene (**8**),[10] 18 mL of 0.5 M $NaHCO_3$, and 60 mL of CH_2Cl_2, and stirred in an ice bath. The ice bath was then removed and the mixture was stirred an additional 2 h. The solution was washed with saturated $NaHCO_3$ (2 × 20 mL), H_2O (1 × 20 mL), and saturated NaCl (1 × 20 mL), dried over anhydrous potassium carbonate, and concentrated under reduced pressure to yield epoxide **1** (0.8 g). VPC analysis showed the material to be >95% pure and it was used without further purification:[11] IR (neat) 2940, 1450, 1372, and 855 cm^{-1}; NMR δ 0.6 (br m, 1 H) and 1.0 (n, m, 1 H) (cyclopropyl protons), 1.07 (s, 6 H, CH_3CCH_3), 1.27 (s, 3 H, CH_3CO), 1.67 (t, 2 H superimposed on br m, 2 H, CH_2CH_2), 3.0 (d, 1 H, J = 2 Hz, HCO); MS *m/e* (rel intensity) 152 (7), 134 (73), 132 (19), 120 (20), 119 (100), 117 (34), 91 (67), 79 (15), 77 (23).

Rearrangement of Epoxide 1 with Zinc Bromide. Approximately 20 mg of $ZnBr_2$ (Fisher certified, not fused) was added to 3 mL of toluene which had been distilled and stored over molecular sieves. The mixture was brought to reflux with vigorous stirring in an apparatus which had been well flushed with nitrogen and equipped with a drying tube. Three-quarters of a mixture of epoxide **1** (150 mg, 0.98 mmol) and 3 mL of toluene was added immediately. After 10 min the remaining one-quarter was added over a 10-min period. Forty minutes after initial oxide addition, the reaction mixture was cooled, taken up in 30 mL of ether, washed successively with water (2 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and saturated NaCl (1 × 10 mL), and dried over anhydrous Na_2SO_4. Partial removal of solvent under reduced pressure afforded an oily residue from which 2-methyl-4-isopropylcyclohex-3-en-1-one (**9**)[15] was isolated by preparative VPC: IR (CCl_4) 2975, 1720, 1360, 1200, 1180 (d), 970 and 930 cm^{-1}; UV (95% EtOH) λ_{max} 290 nm (Σ = 90.9); NMR δ 1.04 (d, 6 H, J = 7 Hz, CH_3CCH_3), 1.14 (d, 3 H, J = 7 hz, CH_3C–), 2.3 (quintet, 1 H, J = 7 Hz), 2.46 (n, m, 4 H), 2.88 (br q with additional splitting HCC=O), 5.37 (n, m, 1 H, HC=C); MS *m/e* (rel intensity) 153 (4), 152 (42), 135 (5), 100 (65), 109 (10), 96 (11), 95 (100), 81 (30), 68 (10), 67 (25), 55 (11). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.08; H, 10.41.

2-Methyl-4-isopropylcyclohex-2-en-1-one (10). A mixture of ketone **9** (4.4 mg, 2.9×10^{-2} mmol), a trace of *p*-toluenesulfonic acid monohydrate, and $CHCl_3$ (3 mL) was refluxed for 30 min, taken up in 30 mL of ether, and worked up as previously described for the $ZnBr_2$ rearrangement to yield an oily residue. One major product (>95% of total volatiles) was isolated by VPC and shown to be ketone **10**: UV (95% EtOH) λ_{max} 227 nm; IR[12] 2950, 1680 (C=O), 1355 and 1375 (d), 1125, 1103, 1072 (d) cm^{-1}; MS[13] *m/e* (rel abundance) 153 (9), 152 (57), 137 (9), 111 (10), 110 (100), 109 (58), 97 (23), 96 (19), 95 (73), 81 (43).

Acknowledgment. We thank Dr. F. Bayer for determination of the 100-MHz NMR Spectra.

Registry No.—**1**, 64130-68-3; **8**, 554-61-0; **10**, 41469-46-9.

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(9) It should be noted that 90% of the products from this reaction are derived from normal opening of the epoxide to yield a tertiary carbonium ion.
(10) Supplied as a gift by Dr. T. F. Sanderson, Hercules, Inc., Wilmington, Del., 95% pure by VPC and contained ≃2.5% 3,4-carene.
(11) The oxide was very sensitive and underwent some rearrangement/decomposition when collected via VPC.
(12) The IR compared well to a spectra of authentic ketone **10** kindly furnished by Dr. J. G. Witteveen of Naarden International, Holland.
(13) MS was identical to authentic **10** generated with levulinic acid[14] from the 2,4-dinitrophenylhydrazone supplied as a gift by Professor T. S. Sorensen, University of Calgary, Calgary, Alberta, Canada.
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(15) **Note Added in Proof.** After this paper was accepted for publication we became aware of a report of menthenone **9** by W. Kraus and G. Zartner, *Tetrahedron Lett.*, 13 (1977), in which **9** was reported in low but unspecified yield by rearrangement of fenchone. The compound was characterized only by two NMR bands and two IR bands. These spectra data do not appear compatible with **9**. Essentially no experimental was given.

Exothermic Cyclic Peroxide Reactions. Decomposition of a 1,2,4-Trioxane

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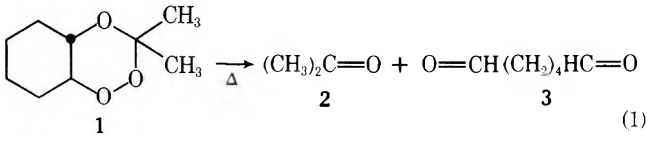
Received July 12, 1977

Recent reports on the thermolysis of cyclic peroxides[1,2] and the suggestion that the 1,2,4-trioxane ring may be a key chemiluminescent intermediate[3] prompt us to communicate our results on the thermolysis of *trans*-4,4-dimethyl-2,3,5-trioxabicyclo[4.4.0]decane (**1**). Peroxides containing the



(1)

1,2,4-trioxane ring system have been prepared previously.[4] However, the products and the kinetic behavior of this molecular class were not reported. In this note we relate our findings on the thermal behavior of 1,2,4-trioxane **1**.

Degassed solutions of peroxide **1** in octane or diphenyl ether were thermolyzed at temperatures ranging from 160 to 189 °C. Analysis of the resulting product mixture by mass and NMR spectroscopy and gas chromatography revealed acetone (**2**) and adipaldehyde (**3**) (see eq 1). The yield of acetone was essentially quantitative; however, the amount of aldehyde **3** formed was dependent upon the extent of the reaction. Extrapolation to very low conversion indicated that the adipaldehyde was formed in ~95% yield. Independent control experiments confirmed that aldehyde **3** was unstable under the reaction conditions.

Investigation of the kinetics for the decomposition of peroxide **1** indicated that the rate of reaction was cleanly first order in peroxide concentration for at least four half-lives. Moreover, it was observed that the addition of *n*-butyl mercaptan did not inhibit the thermal decomposition of **1** (see Table I). The activation parameters for the thermal cleavage of peroxide **1** were determined by investigating the effect of temperature on the observed rate of this reaction. Least-squares analysis of the thermal rate data indicated that $\Delta G^{\ddagger}$ for the rate-determining step of this reaction is 39.9 ± 1.4 kcal/mol at 175 °C.

The results of the investigation of the rate and products of the thermal decomposition of peroxide **1** are consistent with the unimolecular thermal cleavage of the oxygen–oxygen bond as the initial bond-breaking step. The activation energy and the small rate enhancement in more polarizable solvents,[5] as well as the products observed, are in agreement with this

Scheme I

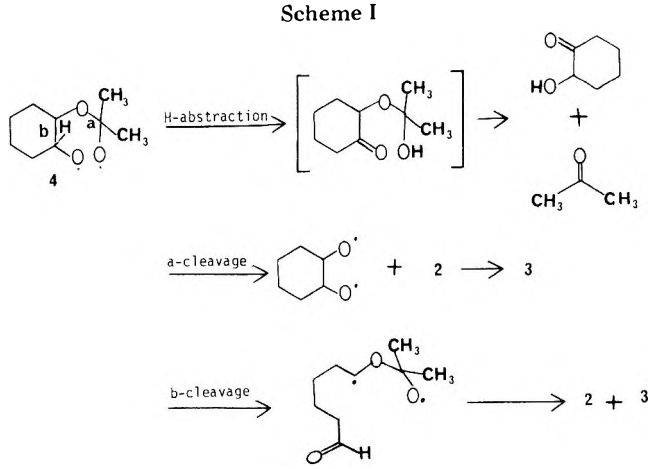


Table I. Thermal Reaction Rate of Peroxide 1

Solvent[a]	Temp,[b] °C	Added substrate	$k \times 10^5$, s^{-1}
Octane	188.9		48.4
Octane	181.9		22.4
Octane	180.0	*n*-Butyl mercaptan[c]	16.4
Diphenyl ether	172.0		61.6
Octane	169.4		7.54
Octane	161.0		2.73

[a] Peroxide concentration was typically 2.5×10^{-2} M. [b] Temperature was regulated to within 0.2 °C. [c] The mercaptan concentration was 5×10^{-2} M.

conclusion. The 1,6 diradical formed from this bond cleavage (**4**) has several reaction paths open to it.

Hydrogen atom abstraction through a six-membered ring transition state is a common reaction of alkoxy radicals. If this were to occur from diradical **4**, we anticipate that adipoin (**5**) would result (see Scheme I). No **5** was found in the reaction mixture. Moreover, it was determined that the adipoin was stable under the reaction conditions. The lack of adipoin formation can be understood if the lifetime of diradical **4** is extremely short. This would be the case if a fast irreversible reaction of **4** were occurring.

A second common reaction of alkoxy radicals is α cleavage to form carbonyl compounds. Biradical **4** must break two α bonds to form the observed products. Three choices for the sequence of bond-breaking steps from this intermediate seem apparent. First, if the bond labeled a (see Scheme I) cleaves first, acetone and a 1,4 biradical will be formed. It should be noted that this 1,4 biradical is the anticipated intermediate in the chemiluminescence of the corresponding 1,2-dioxetane.[6] Alternatively, initial cleavage of the bond labeled b would generate the 1,4 biradical, resulting from the as yet unknown 1,3-dioxetane ring system. Finally, bonds a and b could cleave simultaneously, generating the observed products in one step from the 1,6 biradical. Our results cannot distinguish between these possible reaction pathways.

Peroxide **1** is potentially a chemiluminescent intermediate.[3] Group equivalent calculations[7] indicate that the reaction of **1** to **2** and **3** is exothermic by ~37 kcal/mol. Inclusion of the observed activation energy suggests that ~77 kcal/mol is available for the formation of electronically excited states. This quantity is probably sufficient to populate the triplet state of simple carbonyl compounds with reasonable efficiency. Moreover, if the suspected biradical intermediate (**4**) goes on to product by cleaving bond a, a mechanistic pathway consistent with previous light-forming reactions is available. Unfortunately, the high temperatures required to decompose peroxide **1** mitigate against the detection of a low yield of electronically excited states. The lifetime of carbonyl excited states is shortened at high temperatures so that radiative and energy-transfer processes are at a competitive disadvantage. We did not observe any chemiluminescence that we could assign to the unimolecular decomposition of **1**.

In summary, we have observed that upon thermolysis the relatively stable cyclic peroxide **1** undergoes unimolecular cleavage to form carbonyl compounds **2** and **3** with high efficiency. In addition, the suspected intermediate biradical formed from homolysis of the oxygen–oxygen bond must rearrange rapidly (most probably) by an α-cleavage reaction. Finally, no chemiluminescence was observed during this reaction, although sufficient energy is available to form the lowest triplet state of the observed products.

Experimental Section

NMR spectra were determined with Varian T-60 and EM-390 spectrometers using tetramethylsilane as an internal standard. IR

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spectra were recorded on a Perkin-Elmer 137 instrument. Analytical gas chromatography was carried out on a Varian 2700 all-glass chromatograph equipped with flame ionization detectors, using a 6 ft × 0.25 in. o.d. glass column with 3% SE-30 on Chromosorb Q at 175 °C. All solvents were Aldrich spectrophotometric grade and were used without further purification.

***trans*-4,4-Dimethyl-2,3,5-trioxabicyclo[4.4.0]decane (1).** Peroxide 1 was prepared by the procedure of Payne and Smith.[8] Purification was accomplished by distillation [bp 45–50 °C (0.5 mm)], followed by repeated recrystallization from pentane to yield 15% of the analytically pure peroxide: mp 24–25 °C; IR (CCl_4) 3.3, 7.3–7.4 (*gem*-dimethyls), 8.2, 9.3, 10.6 μm; NMR (CCl_4) δ 1.3 (s, 3 H), 1.6 (s, 3 H), 3.68 (m, J = 11, 8, 3.5 Hz).

Procedure for Determination of Reaction Rate. Solutions of peroxide 1, typically 2.5×10^{-2} M, and an internal standard, usually decane, were prepared in Pyrex test tubes. The samples were degassed at 5×10^{-4} mm through three freeze–pump–thaw cycles and sealed under vacuum. The tubes were then thermolyzed and analyzed at intervals by gas chromatography as described. The rate of reaction of the peroxide and appearance of acetone were both first order. The rate constants were extracted from these data by least-squares analysis and are reported in the Table I.

Acknowledgment. This work was supported in part by the Office of Naval Research and the donors of the Petroleum Research Fund, administered by The American Chemical Society.

Registry No.—**1**, 64235-36-5; **2**, 67-64-1; **3**, 1072-21-5.

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β Radiolysis of Crystalline ^{14}C-Labeled Amino Acids

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Received July 5, 1977

In an investigation of the possible validity of the Vester–Ulbricht β-decay parity violation mechanism[1-3] for the abiotic origin of molecular chirality, one of us has recently shown[4,5] that 10–20% net longitudinally polarized 120-keV electrons produced in a linear accelerator caused the asymmetric degradation of DL-leucine. "Natural" antiparallel spin-polarized electrons preferentially degraded the D-leucine component of the racemate, and parallel spin electrons selectively destroyed the L enantiomer. This was the first positive demonstration of asymmetric degradation by β particles since Garay's 1968 report[6] that 0.36 mCi of $^{90}SrCl_2$ in aqueous solution caused more rapid decomposition of dissolved D-tyrosine than of L-tyrosine. Earlier studies[1-3,7] and our subsequent attempts[8,9] to modify and extend Garay's experiments to other amino acids, both solid and dissolved, using a 61 700-Ci ^{90}Sr–^{90}Y source at Oak Ridge National Laboratory led to no observable asymmetric radiolyses. More recently, Darge and co-workers[10] made the remarkable report that DL-tryptophan in frozen aqueous solution suffered 33% total degradation and (based on its optical rotation of 0.0007 ± 0.0004°) a 19% optical enrichment of the D enantiomer during its 12-week exposure to 0.63 mCi of dissolved [^{32}P]phosphate. In view of the several positive reports of asymmetric β radiolysis reviewed above, we have been encouraged to examine for β-induced optical activity a number of ^{14}C-labeled DL amino acids of high specific radioactivity (~300–600mCi/mol) prepared 17–25 years ago at the Lawrence Berkeley Laboratory, University of California.

The racemic amino acids studied and the radiochemical and analytical data pertaining to them are recorded in Table I. Three of the amino acids listed in Table I (DL-Ala, DL-Asp, and DL-Nva) have been examined previously[11] for optical activity (using ORD measurements) and percent decomposition (using the amino acid analyzer), with the observation of no selective radiolysis. In the present study we have used quantitative gas chromatography (GC) as our analytical criterion for both the enantiomeric composition of the undecomposed amino acid residues as well as for percent degradation (using the "enantiomeric marker" technique[12]). GC not only provides the important advantage (over optical rotation) of looking at *only* the residual enantiomers of interest (uncontaminated by accompanying degradation products which may or may not be optically active) but is capable, particularly with microquantities, of superior accuracy and precision (~0.2%)[13] in the quantitative analysis of enantiomers. The DL amino acids in Table I were converted to their *N*-trifluoroacetyl isopropyl esters as previously described[13] and analyzed in replicate with the aid of a digital electronic integrator,[13] using 150 ft × 0.02 in stainless steel capillary GC columns[13] coated with the optically active GC phases *N*-lauroyl-L-valine *tert*-butylamide.[14] or *N*-docosanoyl-L-valine *tert*-butylamide.[15] All GC analyses were interspersed "back-to-back" with an equal number of replicate GC analyses of the corresponding nonradioactive, authentic DL amino acid as a control. For comparison purposes, Table I also summarizes radiochemical, percent decomposition, and enantiomeric composition data, similarly obtained, for a number of labeled D and L amino acids, which had been prepared by optical resolution of several of the racemic amino acids in Table I.

The enantiomeric compositions in Table I indicate that the D/L ratios of the radioactive DL amino acids examined are 50:50, within experimental error, and that they suffered no asymmetric degradation, despite self-radiolyses as high as 67%. The enantiomeric compositions of the resolved amino acids show further that racemization does not necessarily accompany self-radiolysis in the dry state, although comparison of the enantiomeric compositions noted for D-norvaline-*3*-^{14}C and D-leucine-*3*-^{14}C with those estimated from the original optical rotations of the samples suggests that some racemization may be possible. From the specific radioactivity of the samples and their ages, one can calculate the number of β particles emitted during the lifetimes of the samples. From these numbers (not shown) and the percent decompositions, one can calculate the number of molecules decomposed per β particle, which proves to vary between about 6000 and 36 000 among our samples. These numbers are higher than the ~3000 molecules decomposed per electron observed during our previously reported[4] asymmetric degradations of DL-leucine with longitudinally polarized linear accelerator electrons. The variability in the percent decomposition and hence the number of molecules decomposed per electron, as well as the *G* values observed for comparable samples (e.g., D-, L-, and DL-valine-*4,4'*-^{14}C, D- vs. DL-leucine-*3*-^{14}C, etc.), is noteworthy and may be due, we suspect, to the variability of trace impurities, including moisture, in the 17–25-year-old samples. Finally, the racemic nature of the radiolyzed DL amino acids in Table I further indicates that microbial degradation could not have been operative during the lifetimes

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Table I

Amino acid	Registry no.	Radioactivity, mCi/mol	Age,[a] years	Total dose, rads $\times 10^{-7}$	Percent decomposed	Molecules decomposed per electron $\times 10^{-4}$	G[b]	Enantiomeric composition %D	%L	SD[d]
DL-Alanine-2-^{14}C	4548-47-4	285	16.9	5.05	26.5	2.84	56.8	50.06[c]	49.94	±0.85
DL-Valine-4,4'-^{14}C	5776-57-8	316	25.8	6.51	30.0	1.90	38.0	50.19[c]	49.81	±0.20
DL-Norvaline-3-^{14}C	3409-47-0	574	24.9	11.41	17.4	0.63	12.6	49.94[c]	50.06	±0.18
DL-Leucine-3-^{14}C	3409-50-5	446	24.0	7.63	67.8	3.26	65.2	50.15[c]	49.85	±0.22
DL-Norleucine-3-^{14}C	64235-74-1	551	24.9	9.78	24.1	0.90	18.0	50.10[c]	49.90	±0.17
DL-Aspartic-4-^{14}C acid	19701-77-0	319	24.1	5.40	~50	3.35	67.0	50.23[c]	49.77	±1.02
D-Valine-4,4'-^{14}C	64235-81-0	316	21.3	5.37	31.2	2.39	47.8	100.00	0.00	
L-Valine-4,4'-^{14}C	64235-72-9	316	21.3	5.37	47.1	3.62	72.4	0.00	100.00	
D-Norvaline-3-^{14}C	64235-71-8	574	20.5	9.39	21.1	0.92	18.4	93.95	6.05	±0.21
L-Norvaline-3-^{14}C	64235-70-7	574	20.5	9.39	20.3	0.89	17.8	0.87	99.13	
D-Leucine-3-^{14}C	64235-69-4	446	20.6	6.55	39.5	2.22	44.4	92.55	7.45	±0.11
D-Norleucine-3-^{14}C	64235-68-3	551	20.6	8.09	25.9	1.17	23.4	99.80	0.20	
L-Norleucine-3-^{14}C	64235-67-2	551	20.6	8.09	18.6	0.84	16.8	0.80	99.20	

[a] Between date of preparation and date of analysis. [b] Molecules decomposed per 100 eV, assuming average energy per $\beta = 5.0 \times 10^4$ eV. [c] Corrected to a D/L ratio of 50:50 for composition of authentic DL standard. [d] SD denotes standard deviation for 3–5 replicate GC analyses.

of the samples, since if it had an excess of D enantiomer it should be observed in the residual materials.

Even though ^{14}C β particles are relatively low energy (endpoint energy 155 keV,[16] mean energy ~50 keV), their polarization is substantial. Both theoretically and experimentally,[17] $\beta^{\pm}$ particles emitted with velocity v during weak nuclear decays have a helicity (longitudinal polarization along their direction of motion) of $\mp v/c$. This is a direct consequence of the two-component neutrino theory which predicted the nonconservation of parity.[18] Since the kinetic energy of the electron is related to its rest energy mc^2 by eq 1,[19] it follows that v/c is given by eq 2. Since the rest energy mc^2 of the electron is 511 keV,[20] this implies a polarization for ^{14}C betas of 64.1% at the endpoint energy and 41.3% at the middle (50 keV) of the energy spectrum. Subsequent ionization processes which slow down the primary electron decrease its energy on the average only by ~30 eV per ion pair produced,[21] and furthermore it is known[22] that such ionizations leave the longitudinal polarization of the primary electron virtually unchanged until it has been slowed down to a few keV.[23] We thus conclude that the polarization of the primary electrons available for initiating chiral destruction of the substrate in the ^{14}C experiments is somewhat greater than the polarization (10–20%) of the electrons employed in the accelerator experiments.[4,5]

$$T = mc^2[(1 - v^2/c^2)^{1/2} - 1] \quad (1)$$

$$v/c = (2T/mc^2)^{1/2}(1 + T/2mc^2)^{1/2}/(1 + T/mc^2) \quad (2)$$

Thus, the failure to observe asymmetric β radiolysis in the solid DL amino acid samples listed in Table I, as compared to the small but successful asymmetric degradations previously induced[4,5] in DL-leucine by the 10–20% net longitudinally polarized linear accelerator electrons, is at first appearance puzzling. We believe, however, that the discrepancy may be rationalized as follows. As is apparent (Table I) from the large number of molecules decomposed for each ^{14}C beta emitted, the majority of the degradations must be engendered by secondary electrons produced by numerous subsequent ionizations caused by the primary ^{14}C β particles. The degree of polarization, if any, of such secondary electrons is not known[3] but presumably it is at best considerably less than that of the primary β particles, and furthermore the energies of the secondary electrons (~30-eV average[21]) are in a range more suitable for initiating chemical changes.[24] For these reasons, it seems possible that the differing sample geometries in the two types of experiments might be crucial. In the accelerator experiments the amino acid target was a thin layer in a plane perpendicular to the impinging 120-keV electron beam, while the ^{14}C amino acids were thick bulk samples isotropically irradiated by internally produced β particles. The latter geometry clearly allows for the preferential production and intervention of less polarized (or unpolarized) secondary electrons, which in turn cause greater degradation of a less asymmetric (or totally symmetric) nature. This possibility is emphasized by the fact that up to 36 000 molecules were decomposed per primary β particle in the ^{14}C-labeled samples (Table I), whereas only ~3000 molecules per (higher energy) electron were destroyed in the accelerator experiments.[4,5] Another difference of possible significance is the differing time scale involved in the two types of experiment. The accelerator samples were irradiated for a matter of hours only and were analyzed immediately thereafter, whereas the ^{14}C-labeled samples suffered self-radiolysis during several decades prior to their GC analyses. Clearly the possibility of migration within the crystal lattice of the initial degradation fragments and possible secondary decompositions subsequently engendered by them is much greater in the ^{14}C samples. Such presumably symmetrical processes could conceivably reduce the net asymmetric effect to undetectable levels. It should be mentioned finally that circularly polarized bremsstrahlung produced by the initial longitudinally polarized β particles, which had been originally postulated[1-3] as the source of asymmetric *photochemical* effects which might produce optical activity, has recently been shown[25,26] on energetic grounds to be ineffective in engendering even significant gross degradation of the target sample. Other problems regarding the β-decay mechanism for the origin of optical activity involving ^{14}C and ^{40}K β particles have recently been discussed by us.[27]

Acknowledgment. We are indebted to the National Aeronautics and Space Administration (W.A.B.) and to the Division of Biomedical and Environmental Research of the U.S. Energy Research and Development Administration (H.P.N and R.M.L.) for their partial support of the above investigation.

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Abnormal Products in the Siegrist Reaction Involving Ortho-Fluorinated Intermediates[1]

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Received June 3, 1977

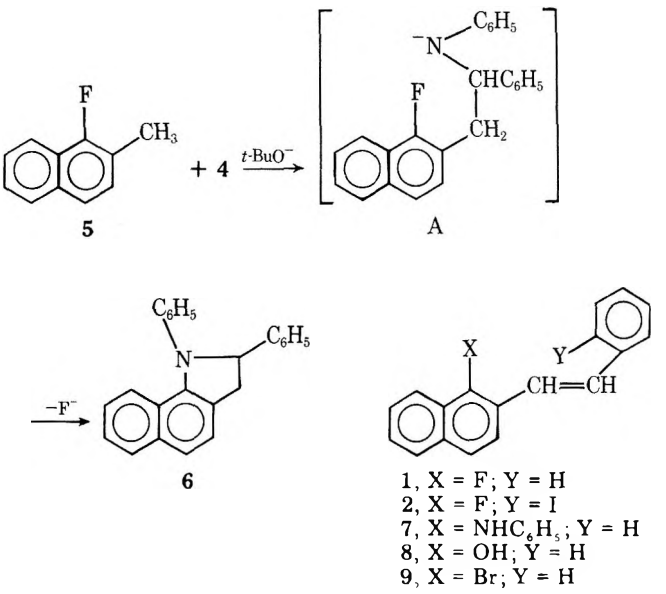
The syntheses of *trans*-1-(1 fluoro-2-naphthyl)-2-phenylethylene (**1**) and *trans*-1-(1-fluoro-2-naphthyl)-2-(*o*-iodophenyl)ethylene (**2**) via the Wittig reaction as intermediates for the attempted photochemical synthesis of 7-fluorobenz[*a*]anthracene (**3**) have been described.[3] Unfortunately, insufficient **3** was made (only via **2** as use of **1** failed) for adequate testing for possible carcinogenic activity. Because of our interest in preparing larger amounts of **3**, we wished to develop improved methods for the synthesis of **1** and **2**.

A route to substituted stilbenes which involves condensation of methylated aromatic nuclei with benzalaniline (**4**) in the presence of potassium *tert*-butoxide (eq 1) has been studied[4] and applied to the facile synthesis of hexahelicene and other helicenes.[5] However, no example involving an ortho halogen-substituted reactant has been reported.

$$\underset{}{ArCH_3} + \underset{\mathbf{4}}{C_6H_5N{=}CHC_6H_5} \rightarrow ArCH{=}CHC_6H_5 + C_6H_5NH_2 \quad (1)$$

Consequently, we attempted to react 1-fluoro-2-methylnaphthalene (**5**) and **4** as above. None of the expected **1** was obtained. Instead, a complex mixture was produced from which small amounts of 2,3-dihydro-1,2-diphenylindole (**6**), *trans*-(1-anilino-2-naphthyl)-2-naphthyl)-2-phenylethylene (**7**), and *trans*-1-(1-hydroxy-2-naphthyl)-2-phenylethylene (**8**) were isolated. A similar reaction with 1-bromo-2-methylnaphthalene and **4** afforded *trans*-1-(1-bromo-2-naphthyl)-2-phenylethylene (**9**) in 58% yield with no evidence for the formation of nitrogenous products.

Scheme I



The formation of **6** probably occurs by intramolecular nucleophilic displacement of fluoride ion by anion A, produced by the addition of the 1-fluoro-2-naphthylmethyl anion to **4**, as shown in Scheme I. The formation of **7** evidently involves a base-catalyzed cleavage of a C–N bond in **6** to form **7**. We have shown that under the reaction conditions **6** is converted to **7**. The formation of **8** probably occurs by displacement of the fluorine in **5** by *tert*-butoxide followed by a normal Siegrist reaction and pyrolytic cleavage of the resulting *tert*-butyl ether.

Interestingly, the elimination of aniline to form **9** occurs more rapidly than intramolecular displacement of bromide ion in the bromo intermediate corresponding to A. Evidently, the bromine in **9** is relatively much more stable to attack by *tert*-butoxide ion or to intramolecular attack by a nitrogenous anion similar to A than is the fluorine in **1** (or A). To our knowledge the contrasting results in the reactions of **4** with 1-fluoro-2-methylnaphthalene (**5**) and with 1-bromo-2-methylnaphthalene provide the first evidence that the intramolecular nucelophilic displacement of fluoride occurs more easily than that of bromide. Some, but not all, evidence shows that aryl fluorides are more reactive than aryl bromides in intermolecular nucleophilic substitution.[6] The same conclusion was reached in a study[7] on the action of potassium *tert*-butoxide in Me_2SO on chloro-, bromo- and iodonaphthalenes which showed that the reactions proceeded via 1,2-naphthyne to give mixtures of 1- and 2-*tert*-butoxynaphthalenes, whereas both 1- and 2-fluoronaphthalene formed 1- and 2-*tert*-butoxynaphthalenes, respectively, by direct displacement of fluoride.

In order to obtain evidence as to the mechanism of formation of **6** and **7** in the Siegrist reaction, we prepared **1** as described[3] from **5**,[8] prepared in improved yield (63%) by using the diazonium hexafluorophosphate[9] instead of the diazonium tetrafluoroborate.[8] On heating **1** with aniline under conditions identical to those involved in the reaction of **4** and **5**, there was obtained neither **6** nor **7**, and 85% of **1** was recovered. This fact supports the intramolecular mechanism for the formation of **6** shown in Scheme I.

When *o*-fluorotoluene was treated with **4** a 28% yield of 1-(o-fluorophenyl)-2-phenylethylene (**10**) was obtained, but no attempt to maximize the yield nor to isolate other components was made. Thus, the fluorine in **10** is less reactive than the fluorine in **1** under Siegrist conditions.

0022-3263/78/1943-0524$01.00/0

Experimental Section[10]

1-Fluoro-2-methylnaphthalene (5). Diazotization of 1-amino-2-methylnaphthalene[11] and conversion into the diazonium hexafluorophosphate were carried out as described.[9] Pyrolysis at 170–180 °C in mineral oil for 30 min afforded crude **5**, which on redistillation afforded 63% of twice distilled **5**, bp 62 °C at 0.5 mm.[8]

Reaction of 5 with Benzalaniline (4). A mixture of 1.6 g of **5**, 1.8 g of **4**, 2.8 g of *t*-BuOK, and 15 mL of DMF was heated at 95 ± 3 °C for 90 min, cooled, and added to 150 mL of 10% HCl. The organic product, isolated as usual, was dissolved in 20 mL of ethanol. On cooling, a colorless solid separated and was recrystallized from benzene–petroleum ether (30–60 °C) to yield 420 mg (18%) of **7**, mp 167–168 °C: MS *m/e* 321;[12] NMR [$(CH_3)_4Si$, $CHCl_3$] δ 5.65 (s, 1, NH, exchanged by D_2O), 6.51–8.18 (m, 18, ArH, CH=CH). Further crystallization of the material in the mother liquor from benzene–petroleum ether (30–60 °C) afforded 100 mg (3%) of colorless **6**, mp 164–165 °C, giving blue fluorescence in benzene: MS *m/e* 321; NMR 2.98 (q, 1, J_{ac}, −4 Hz, J_{bc} = −15 Hz), 4.06 (q, 1, J_{ab} = −10 Hz, J_{bc} = −15 Hz), 5.15 (q, 1, J_{ac} = −4 Hz, J_{ab} = −10 Hz), 6.78–7.95 (m, 16, ArH). Anal. Calcd for $C_{24}H_{19}N$: C, 89.7; H, 5.9; N, 4.4. Found: C, 90.2; H, 5.9; N, 4.0.

Alkaline extraction of the material remaining in the mother liquor followed by acidification of the extract and crystallization from benzene–petroleum ether (30–60 °) afforded 200 mg (7%) of **8**: mp 150.5–151.5 °C; MS *m/e* 246;[12] NMR 5.56 (s, 1, OH exchangeable with D_2O), 6.90–8.23 (m, 13 H, ArH, CH=CH). Anal. Calcd for $C_{18}H_{14}O$: C, 87.8; H, 5.7. Found: C, 88.2; H, 5.8.

After heating a solution of 0.25 g of **1**, prepared as described[3] with 0.09 g of aniline and 1.1 g of *t*-BuOK in 10 mL of DMF for 12 h at 100–110 °C, most (85%) of the **1** was recovered, and no trace of **6** or **7** was found using TLC (neutral alumina).

***trans*-1-(1-Bromo-2-naphthyl)-2-phenylethylene (9).** A mixture of 4.4 g of 1-bromo-2-methylnaphthalne,[11] 3.6 g of **4**, 4.5 g of *t*-BuOK, and 80 mL of DMF was heated at 95 °C for 1 h, cooled, and poured into 120 mL of 10% HCl. On crystallization from ethanol of the organic products, isolated as usual, there was obtained 3.6 g (58%) of **9**: mp 115–116 °C (lit.[13] mp 121–122 °C); MS *m/e* 308, 310.[12]

1-(*o*-Fluorophenyl)-2-phenylethylene (10). In a Siegrist reaction similar to those described above (1 h at 95 °C), *o*-fluorotoluene was converted in 28% yield into **10**: mp 103.0–103.5 °C, MS *m/e* 198.[12] Anal. Calcd for $C_{14}H_{11}F$: C, 84.8; H, 5.6; F, 9.6. Found: C, 84.7, H, 5.5; F, 9.6.

The mother liquor on evaporating to dryness gave an impure oil (several spots on TLC) containing nitrogen but no fluorine on elemental analysis. No further attempt was made to purify it.

Registry No.—**4**, 538-51-2; **5**, 573-99-9; **6**, 64345-68-2; **7**, 64345-71-7; **8**, 64345-70-6; **9**, 27854-69-9; **10**, 64345-69-3; 1-bromo-2-methylnaphthalene, 2586-62-1; *o*-fluorotoluene, 95-52-3.

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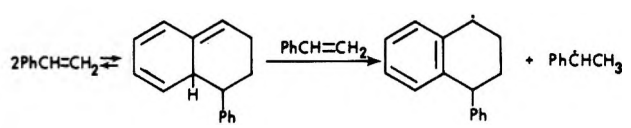
Communications

Thermal Reaction between 5-Methylene-1,3-cyclohexadiene and Styrene[1]

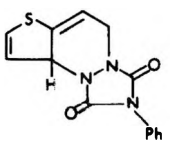
Summary: At 80 °C 5-methylene-1,3-cyclohexadiene reacts rapidly, $t_{1/2} \sim 6$ min, with styrene to produce a 3:1 mixture of 1,2- and 1,3-diphenylpropane in 90% yield. The triene does not initiate the polymerization of styrene.

Sir: The proposal[2] that the monoradical forming step in the thermal polymerization of styrene involves hydrogen atom transfer from a preformed dimer **1** to styrene (Scheme I) has received considerable support.[3] Isolation of **1** has not been accomplished yet, but an analogue **2** has been prepared and shown to initiate the polymerization of styrene.[4]

Scheme I



1



2

3

In another attempt to verify some of the chemistry attributed to **1** the corresponding parent triene, 5-methylene-1,3-cyclohexadiene (**3**), has been prepared and some of its reactions studied. The preparation of **3** by thermolysis of an ester has been reported already.[5] The search for a compound that might decompose at a much lower temperature and allow **3** to be generated slowly in styrene solution led to the alternate synthesis shown in Scheme II. Itaconic anhydride and α-pyrone were heated under N_2 in toluene at 90 °C for 65 h to

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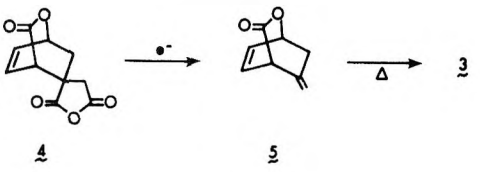
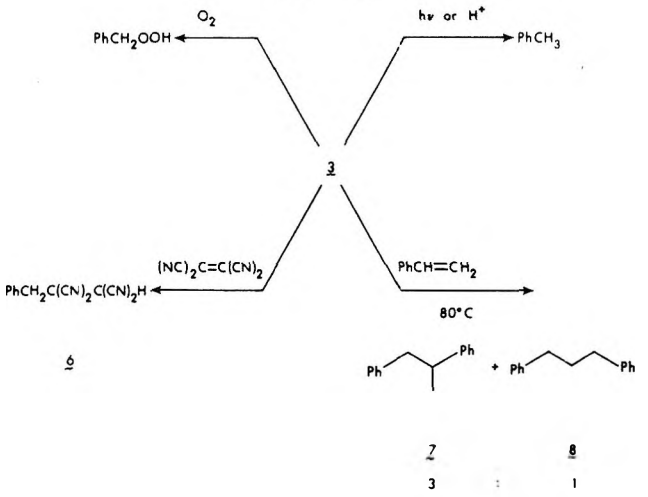
Scheme II



Scheme III



form the adduct **4**,[6,7] mp 144–146 °C, 27%. Electrolysis[9] of **4** produced **5**,[6] mp 11–14 °C, 45%.

The rate of thermolysis of **5** is great enough, at 60 °C $k_1 \sim 2.5 \times 10^{-7}$ s^{-1},[10] so that thermolysis of a $\sim 10^{-1}$ M solution of **5** in styrene should result in formation of radicals at a rate greater than the thermal rate of formation of radicals in styrene, at 60 °C $k_i = 1.3 \times 10^{-10}$ mol L^{-1} s^{-1},[11] if hydrogen atom transfer from **3** to styrene were efficient. However, after heating styrene containing 0.1 M **5** at 80 °C for 2 h only 80% as much of a less crystalline polymer was isolated by precipitation with ethanol as was isolated from control runs. Evaporation of styrene under vacuum left <5% more residue, after correction for remaining **5**, than was left in control runs. Thus, **5** appears to act only as a chain transfer agent and not as an initiator.

Injection of ether solutions of **5** into a gas chromatograph (GC) produced 65% **3**, 5% toluene, and a trace of benzene.[12] Pure (GC) **3**[13] was trapped from the effluent of the GC. Reactions of **3** that were studied are shown in Scheme III. It is quite stable in the absence of oxygen or acid.

In degassed cyclohexane a 10^{-4} M solution of **3** is indefinitely stable at 20 °C and at 60 °C **3** is slowly isomerized to toluene, $t_{1/2} \sim 130$ h. Rapid isomerization, $t_{1/2} = 23$ min, of **3** to toluene occurred in a cyclohexane solution containing 10^{-4} M **3** and 5×10^{-4} M Cl_3CCO_2H at 20 °C. Atmospheric oxygen slowly oxidizes **3** to benzyl hydroperoxide.[14] Photolysis ($\lambda >$ 2800 nm) of **3** in cyclohexane produced toluene as the major product. Treatment of **3** with tetracyanoethylene (TCNE) resulted in a rapid reaction to form the ene adduct **6**[6,15] as the only detectable adduct. Thermolysis of **5** in the presence of TCNE also formed **6**.

At 80 °C there is a rapid reaction, $t_{1/2} \sim 6$ min, between **3** and styrene to form **7** and **8** in a 3:1 ratio in 90% total yield. About 5–8% toluene is formed also. No extra polymer is formed in styrene containing 2×10^{-3} M **3** after 12 min at 80 °C when 60–70% of **3** is consumed. Hydrogen atom transfer from **3** to styrene followed by coupling of the resulting benzyl and 1-phenylethyl radicals could be the route by which **7** is formed, but such a simple radical route to **8** is not available. Also, the lack of formation of extra polymer indicates that if radicals are formed they must all be consumed by coupling and disproportionation before addition to styrene can occur. It is unlikely that this would happen. Both **7** and **8** can be formed by a concerted ene reaction.[16] Reaction of unsymmetrical enophiles with alkenes has been shown to produce mixtures of products.[17]

The experiments reported here provide no evidence that **3** can function as an initiator of styrene polymerization. In this respect the behavior of **3** is quite different from that attributed to **1** and found for the synthetic analogue **2**.[4] Isolation of a trimer corresponding to the coupling product of the radicals shown in Scheme I[18] indicates that **1** and **3** may have one reaction with styrene in common.

A careful kinetic study also has shown that **3**, prepared by an independent route, does not initiate the polymerization of styrene.[19]

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(12) Injection port 400 °C, Carbowax 1000 column, 70 °C. Benzene was identified by its retention time and by its mass spectral cracking pattern. Its mode of formation is unknown.
(13) NMR (C_6D_6) τ 3.87–4.68 (4 H, complex multiplet), 5.25 (2 H, complex multiplet), 6.93 (2 H, complex multiplet); UV λ_{max} (C_6H_{12}) 303 nm (ϵ 4400); IR ν_{max} (CCl_4) 3075 (m), 3035 (s), 1595 (s), 1400 (s), 863 (s), 647 (s) cm^{-1}. The UV data is the same as that previously reported,[5] but the IR data is somewhat different. The mass spectral cracking pattern obtained on electron impact is identical with those of toluene and of cycloheptatriene, but that obtained by chemical ionization (CH_5^+) is different from that of toluene.
(14) The ^{1}H NMR signals due to **3** of a ~0.1 M solution in C_6D_6 containing a drop of D_2O kept under air disappeared over a period of several days and were replaced by signals at τ 2.85 (5 H, m) and 5.31 (2 H, s).
(15) NMR (CD_3COCD_3) τ 2.46 (5 H, s), 4.0 (1 H, s), 6.21 (2 H, s). Material of the same melting point previously isolated was formulated as the Diels–Alder adduct.[5]
(16) For a review of the ene reaction see H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556–557 (1969).
(17) K. Alder and H. von Brachel, *Justus Liebigs Ann. Chem.*, **651**, 141–153 (1962).
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Received August 22, 1977

Radical Production from the Interaction of Closed-Shell Molecules. 5. The Chemistry of Methylenecyclohexadiene[1]

Summary: 5-Methylene-1,3-cyclohexadiene (MCH) has been studied as a model for the Diels–Alder dimer of styrene (AH), which is postulated to be involved in radical production in the

0022-3263/78/1943-0526$01.00/0

Table I. A Comparison of Data for AH and MCH in 8.35 M Styrene at 60 °C

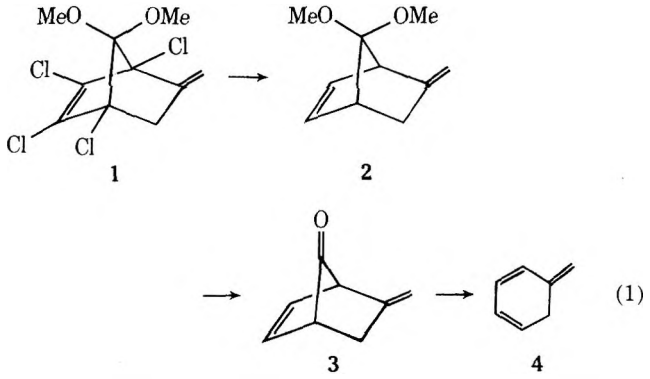
Compd	k_{dis}, M^{-1} s^{-1} [a]	$R_P \times 10^6$ [b]	$\bar{P}_n \times 10^{-4}$ [c]	C [d]	% MAH [e]
AH	0.9×10^{-5} [f]	2.0 [g]	1.0 [g]	1 [h]	1
MCH	5.3×10^{-5} [i]	2.0 [j]	0.2 [k]	9 [l]	<0.01

[a] Pseudo-unimolecular rate constant for disappearance of the compound in styrene, determined using UV absorption. [b] Rate of polymerization of styrene, M s^{-1}. [c] Number-average degree of polymerization. [d] Transfer constant; i.e., the ratio of rate constants for chain transfer and propagation, ref 2b. [e] Percent of the compound that disappears in reactions that produce radicals (other than by transfer) capable of initiating styrene's polymerization. [f] Calculated from the rate of formation of AH assuming a steady-state concentration of 6.5×10^{-5} M, ref 16. [g] For thermal polymerization, ref 15 and 17. [h] Reference 22. [i] From disappearance of MCH followed at 360 nm. [j] Determined by precipitation at 0.0004–0.012 M MCH. [k] At 1×10^{-4} M MCH. [l] Approximate value, see text.

spontaneous polymerization of styrene. Attempts to rationalize the different rates of radical production from MCH and AH are presented.

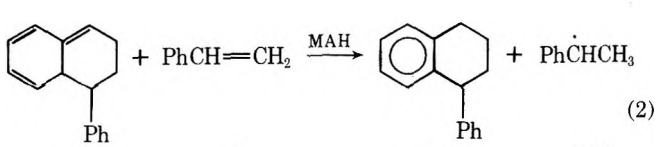
Sir: The acceleration of the homolytic scission of bonds in one molecule by interaction with another molecule is of considerable theoretical[1,2] and practical[3] significance. Of these reactions, the molecule-assisted homolysis (MAH) of a C–H bond in the presence of olefins is the most intriguing to organic chemists, and several such processes have now been identified.[1-4] With the aim of studying a particularly simple example of such a process, we have examined the reactions of 5-methylene-1,3-cyclohexadiene (MCH) with styrene.

The synthesis of MCH (**4**) has been reported by Bailey and Baylouny,[5] but isolation of MCH from the dilute pentane solution obtained in their method requires repetitive GLC. We sought a route involving a less tedious isolation and purification procedure; our synthesis is outlined in eq 1. Compound **1**[6,7] when treated with sodium and *tert*-butyl alcohol in tetrahydrofuran gives a 31% yield of **2**.[8] The ketal **2** can be hydrolyzed to **3** with 3 M H_2SO_4 at room temperature in 60% yield.[9] Ketone **3** decarbonylates under a variety of conditions to give MCH.[10] The most convenient method consists of a bulb-to-bulb transfer of neat ketone at 0.5 mmHg through a tube heated to 250 °C. The product was isolated by GLC.[11]



1 2 3 4 (1)

There is a considerable body of evidence that has been interpreted as demonstrating that the mechanism of initiation of the thermal polymerization of styrene is the MAH reaction of the styrene Diels–Alder dimer, AH, with another styrene molecule, eq 2.[3,12] It appeared likely that MCH would also

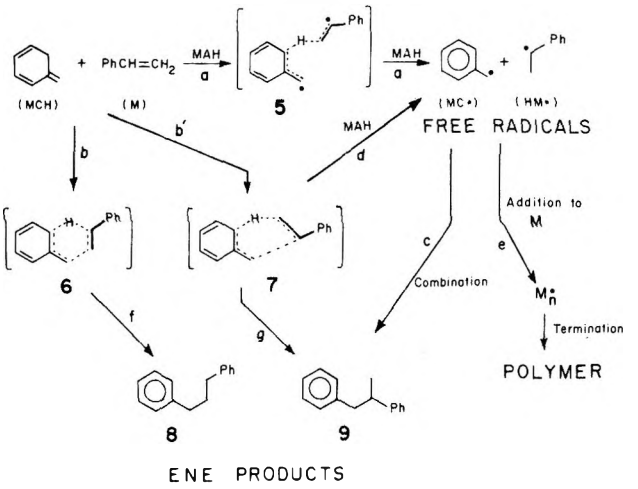


AH M A· HM (2)

undergo an MAH reaction with styrene and initiate polymerization, as shown in Scheme I.

Surprisingly, however, MCH does not initiate the polymerization of styrene. Concentrations of MCH from 0.004 to 0.012 M produce rates of polymerization equal to the thermal rate, within experimental error. Furthermore, methyl acrylate, which does not undergo spontaneous polymerization, is not initiated by concentrations of MCH as high as 0.01 M. However, MCH does disappear rapidly in both styrene and methyl acrylate (as monitored by UV).

Scheme I



Scheme I outlines possible reactions of MCH (or AH). Kopecky and Lau,[13] who independently have found that MCH does not initiate the polymerization of styrene, have reported that MCH undergoes an ene reaction[14] with styrene to give both **8** and **9**. Product **8** can best be rationalized by reactions b and f of Scheme I. Product **9** could arise from analogous processes, eq b′ and g; however, since the parallel reactions of AH and related species[4] lead to scavengable free radicals, product **9** might result from reactions a and c, or b′-d-c as well.

Table I shows a comparison of data for AH and MCH in styrene at 60 °C. Based on the known rate of polymerization of styrene[15] and our measured rate of the pseudo-unimolecular disappearance of AH in styrene, k_{dis}[AH],[16] only a small

$$R_i = \frac{2k_t R_p^2}{k_p^2 [M]^2} = 2k_{dis} f[AH] \quad (3)$$

fraction, $f \simeq 0.011$, of the AH reacts in styrene to give scavengable radicals (cf. eq 3[17]). Most of the AH gives ene products via reactions b, b′, or c in Scheme I. A small amount of AH is consumed by chain transfer.

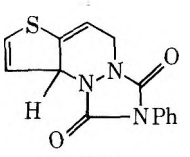
The rate constant for disappearance of MCH in styrene is six times larger than that of AH (Table I). However, a more rapid ene reaction alone cannot account for the lack of detectable free-radical production from MCH. If it is *assumed* that MCH undergoes an assisted homolysis with the same rate constant as does AH, then 10^{-2} M MCH is sufficiently concentrated so that an increased rate of polymerization should be observed. This is true even if a rapid ene reaction (and/or chain transfer) of MCH consumes 99.9% of the MCH and only

0.1% undergoes an MAH reaction. In order to explain the observed lack of initiation, MCH must have a rate constant for MAH reaction that is at least 20 times smaller than that of AH.[18]

Two types of transition states for the MAH reaction of MCH (or AH) could be envisioned: (1) a cyclic, ene-like transition state (7) could give scavengable radicals via eq d;[19] or (2) the MAH transition state might involve an open, extended conformation (5) in which the radical centers are formed far apart. Radicals formed in this process may combine to form ene-type products (eq c) or diffuse apart (eq e) and initiate polymerization.

This formulation of ene and MAH processes suggests a possible rationale for the larger yield of radicals from AH–styrene than from MCH–styrene. The ene reaction is known to be sensitive to steric effects,[20] and models indicate that the repulsive interactions in transition states like **6** or **7** would be greater for AH than for MCH. This may force a larger fraction of the AH–styrene interactions to adopt the extended transition state **5**, or to have more radical character in transition state **7**, giving a greater yield of radicals via reaction d. In addition, it should be noted that the potential MAH steps involve donation of a more labile *tertiary* hydrogen from AH to give a *secondary* benzylic radical, whereas MCH would be required to donate a *secondary* hydrogen to give a *primary* benzylic radical.

As might be expected, MCH is an excellent transfer agent. The transfer constant of MCH is approximately 9 at 60 °C.[21] This is by far the largest transfer constant ever reported for a hydrocarbon. Since the value is so large, it is difficult to measure precisely;[21b] however, there is no doubt that MCH is an excellent transfer agent, as good or better than AH ($C = 1$)[22] or BH ($C = 5$), another model of AH that we reported on previously.[4]



BH

Finally, some comments should be made about the implications of the present work on the mechanism of the thermal polymerization of styrene.[1b] Our *a priori* expectation was that MCH would initiate polymerizations. The fact that it does not can be rationalized in one of two ways. (1) It can be assumed that MCH is a poor model for AH, because ene reactions involve variable transition states with differing amounts of radical character, or because AH donates a tertiary hydrogen and yields a tertiary radical whereas MCH donates a secondary hydrogen to yield a primary radical, or for some other reason. (2) Or the MAH mechanism for the initiation of polymerization of styrene by AH can be rejected. A critical review[1b,3] of the evidence supporting the AH mechanism indicates overwhelming support for the *presence* of AH in thermal polymerizations of styrene and *transfer* by AH, but an absence of *unambiguous* evidence that AH undergoes an assisted homolysis step (eq 2). However, if the AH mechanism for styrene is rejected, it is difficult to suggest an alternative.[1b] (One alternative possibility is the diradical transfer mechanism that we have recently suggested for pentafluorostyrene.[23])

It seems most reasonable and economical at present to continue to accept the Diels–Alder mechanism for styrene, but with the realization that the critical MAH step, eq 2, has *not* been explicitly established. Clearly, the critical experiment is the synthesis and testing of AH itself, and we are now attempting this.[1b]

Acknowledgment. We wish to thank the National Science Foundation for partial support of this work and Dow Chemical Company for a grant to William A. Pryor. We also wish to express our appreciation to Dr. Masashi Iino for preliminary studies, Mary G. Sorci for polymer solution viscosity measurements, and Dr. Eric G. Olsen for helpful suggestions.

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(9) NMR (CCl_4) δ 6.56 (t, 2-H), 5.08 (t, 1-H), 4.83 (t, 1-H), 3.3 (m, 1-H), 3.0 (m, 1-H), 2.9 and 2.6 (m, 1-H), 2.15 and 1.88 (t, 1-H). 2,4-DNP: mp 78–81 °C.
(10) Identified by GC retention time, UV, and NMR. The decomposition of the ketone was first order in CCl_4 solution with a half-life of 4440 s at 93 ± 1 °C and 380 s at 112 ± 1 °C. MCH is both air and acid sensitive and must be handled accordingly.
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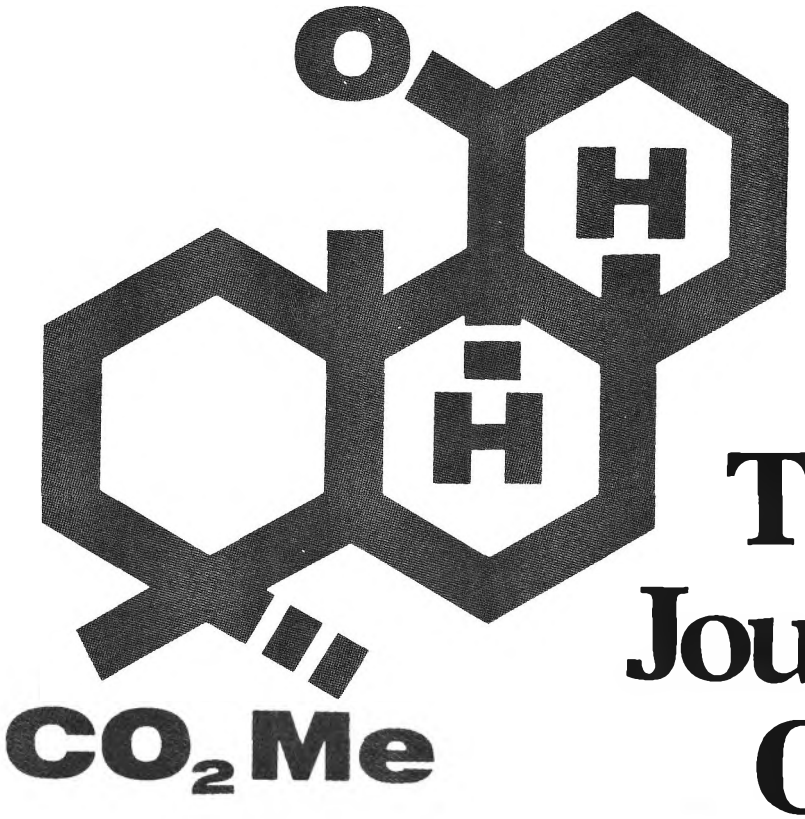

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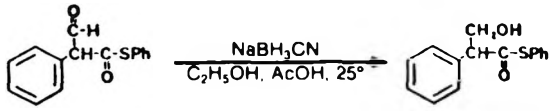

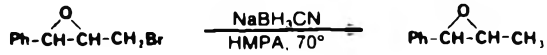

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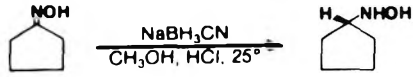

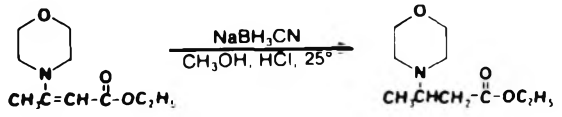

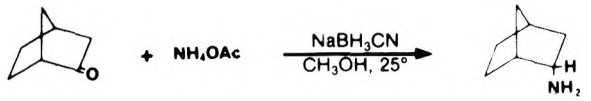

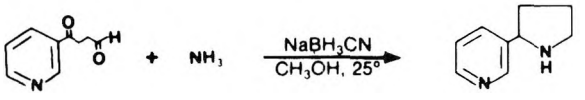

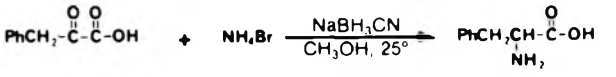

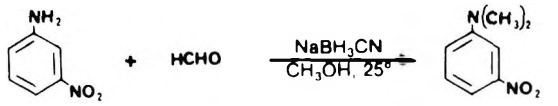

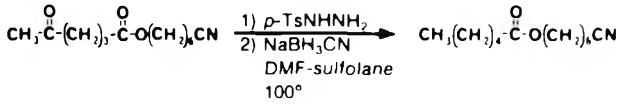

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For a complete list of references, please send for a detailed technical information bulletin. The following are leading references:

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