VOLUME 43 MARCH 31, 1978 NUMBER 7 JOCEAH

THE JOURNAL OF Organic Chemistry

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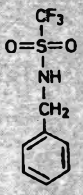
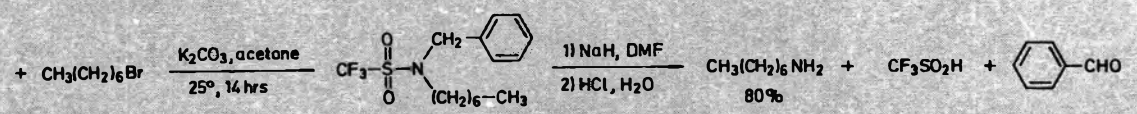
13960 N-Benzyl trifluoromethanesulfonamide purum MP 45-47 (N-Benzyl-triflamide) — 5 g sFr. 32.— US$ 16.00
$CF_3SO_2NHC_7H_7$ $C_8H_8F_3NO_2S$ MW 239.22

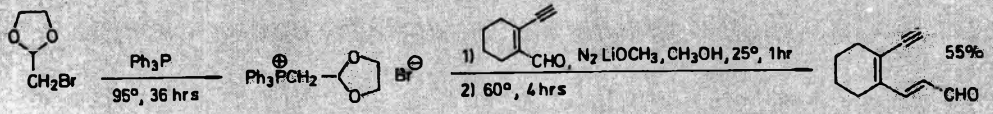


Reagent for a new "Gabriel" synthesis of primary amines. — 25 g sFr. 135.— US$ 62.50
J.B. Hendrickson et al., Tetrahedron (1975) 31, 2517



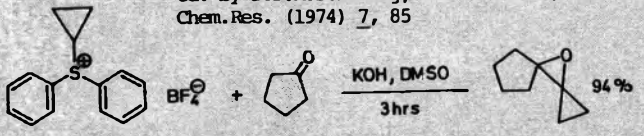
17618 2-Bromomethyl-1,3-dioxolane pract. BP_{12} 65-67°; n_D^{20} 1.4798 — 1 lt ≈ 1.61 kg — 25 ml sFr. 18.— US$ 9.00
$C_4H_7BrO_2$ MW 167.02

Useful synthon for the preparation of α,β-unsaturated aldehydes: T.M. Cresp, M.V. Sargent, P. Vogel, J.Chem.Soc.Perkin I (1974) 39; synthon, for the preparation of 1,4-dialdenyde monoacetals: J.F. Le Borgne, Th. Cuvigny, M. Larchevêque, H. Normant, Tetrahedron Lett. (1976) 1379 — 100 ml sFr. 65.— US$ 32.50

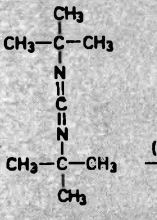


29950 Cyclopropyldiphenylsulfonium tetrafluoroborate pract. MP 135-137° — 1 g sFr. 65.— US$ 32.50
$CH_2CH_2CHS(C_6H_5)_2(BF_4)$ $C_{15}H_{15}BF_4S$ MW 314.15

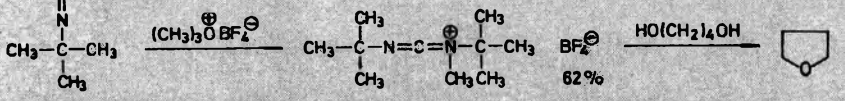
Excellent reagent for the spiroannelation of carbonyl compounds. The ylide derived from this salt effects many different synthetic transformations: M.J. Bogdanowicz, B.M. Trost, Org.Synth. (1974) 54, 27; B.M. Trost, Pure and Appl.Chem. (1975) 43, 563-585; B.M. Trost in "Organic Sulphur Chemistry", ed. by D.J.M.Stirling, Butterworths, London (1975) 237-263; B.M. Trost, Acc. Chem.Res. (1974) 7, 85



34640 N,N'-Di-tert-butylcarbodiimide purum >99%(GLC); BP_{12} 48-50°; n_D^{20} 1.4298; 1 lt ≈ 0.80 kg — 5 ml sFr. 37.— US$ 18.50
$(CH_3)_3C:N:C(CH_3)_3$ $C_9H_{18}N$ MW 140.25

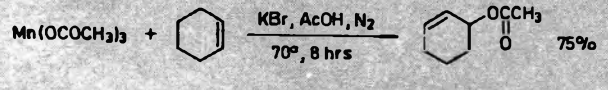


Synthon; dehydrating reagent; starting material for the preparation of N,N'-di-tert-butyl-N-methylcarbodiimidium tetrafluoroborate, a potent agent to effect molecular dehydrations: K. Hartke et al., Liebigs Ann.Chem. (1972) 762, 167; R.C. Schnur, E.E. van Tamelen, J.Am.Chem.Soc. (1975) 97, 464



63538 Manganese (III) acetate pract. (Manganic acetate) — 50 g sFr. 50.— US$ 25.00
$Mn(OCOCH_3)_3.2H_2O$ $C_6H_9MnO_6.2H_2O$ MW 268.10

Reagent for the oxidation of olefins and aromatic hydrocarbons: L. Fieser M. Fieser, "Reagents for Organic Synthesis", 2, 263, 4, 318, 6, 355; John Wiley and Sons, Inc.; J.R. Gilmore, J.M. Mellor, J.Chem.Soc. (C) (1971) 2355



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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 7

MARCH 31, 1978

Impact of High-Lying σ Orbitals and Extensive Through-Bond Interaction on Chemical Reactivity. 1. Convenient Syntheses of Hypostrophene and Its Susceptibility to Rearrangement under Electrophilic Conditions

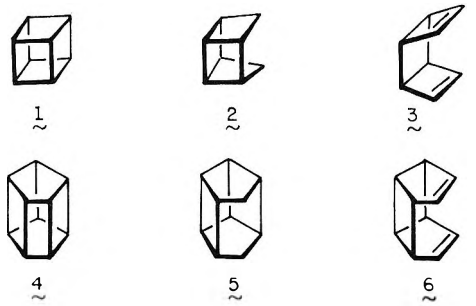
Leo A. Paquette,* Donald R. James,[1] and Gerhard Klein

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received September 15, 1977

Two practical syntheses of hypostrophene (**6**) beginning with cyclopentadiene (14.6% overall) and cyclopentanone (21.6%) are reported. Both routes converge at the stage of keto ketal **8**, which is subsequently photocyclized and transformed to diiodide **14**. Exposure of **14** to sodium–potassium alloy delivers the title diene. When **6** was treated with elemental bromine or *N*-bromosuccinimide in aqueous dimethyl sulfoxide, extensive structural rearrangement occurred with formation of the *endo*-dicyclopentadiene derivatives **17** and **23**, respectively. Under acidic conditions, epoxide **26** was similarly isomerized to diol **30**, the skeletal rearrangement again involving eight of the ten carbon atoms contained in the hypostrophene framework. A possible correlation between the high-lying σ orbitals present in **6**, its marked preference for through-bond instead of through-space interaction, and strain relief is presented in rationalization of this proclivity for deep-seated structural change.

In molecules such as cubane (**1**) and pentaprismane (**4**), two identical alicyclic rings are brought together in face-to-face proximity within a rigid prismatic molecular framework. At least in the case of **1** (**4** remains unknown), such a bonding arrangement engenders sizable strain energy[2] with resultant high chemical reactivity.[3] The state of hybridization demanded by the novel geometry of **1**[4a] is reflected in the high acidity of its protons,[4b] its very low (8.74 eV) first ionization potential,[5] and its behavior on electron impact.[6] Progression through the series **1–3** and **4–6** results in substantial strain



1 **2** **3**

4 **5** **6**

amelioration. The pair of internal hydrogens in secocubane (**2**) are known to cause outward puckering of the upper and lower cyclobutene rings.[7] A comparable steric situation likely prevails in **5**.

The removal of two contiguous lateral bonds in **1** and **4** leads to **3**[8] and **6**,[9] respectively, having pairs of nonconjugated cisoid π orbitals whose inner lobes are tightly compressed. Despite their obvious proximity, however, the double bonds in *syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-diene[10] and hypostrophene[11] experience vastly more effective through-bond interaction than through-space coupling. This results because of the continued presence of exceptionally high-lying σ orbitals which serve to reverse the normal ordering, wherein the out-of-phase linear combination of the two π orbitals is located at higher energy than the in-phase combination.[12] Since few known organic molecules possess structural and stereoelectronic features capable of effectively overriding customary through-space interaction, the reactivities of **3**, **6**, and suitable derivatives thereof merit serious experimental investigation.

Although these interesting molecules hold promise as possible sources of new theoretical and mechanistic understanding, they have been subjected to very limited scrutiny, apparently due to their relative inaccessibility. It is currently recognized that neither diene is capable of ($\pi 2_s + \pi 2_s$) photochemical cyclization, since through-bond coupling destroys the usual symmetry allowedness of this closure. In contrast, the capability of both molecules for sequential degenerate Cope rearrangement of low temperatures is not inhibited.[9,13] Therefore, these substances can endlessly interchange two sets of carbon atoms with regeneration of the original structures. At somewhat more elevated temperatures, **3** is transformed into cyclooctatetraene[14] and **6** gives rise to an isomeric $(CH)_{10}$ hydrocarbon.[9]

In this and the two accompanying reports,[15,16] we have attempted to relieve this imbalance through development of practical synthetic routes to **6**, analysis of its response to electrophilic reagents, and investigation of the solvolytic behavior of appropriately functionalized derivatives of **3** and **6**.

Results

Synthetic Considerations. Pettit's original synthesis of hypostrophene provides the hydrocarbon in 0.7% yield from cyclooctatetraene and is not only costly but also tedious. Therefore, the development of rather less expensive and more flexible routes to **6** was initially investigated. Two series of interconversions were developed to gain access to the pivotal intermediate **8** (Scheme I). The first of these began with cy-

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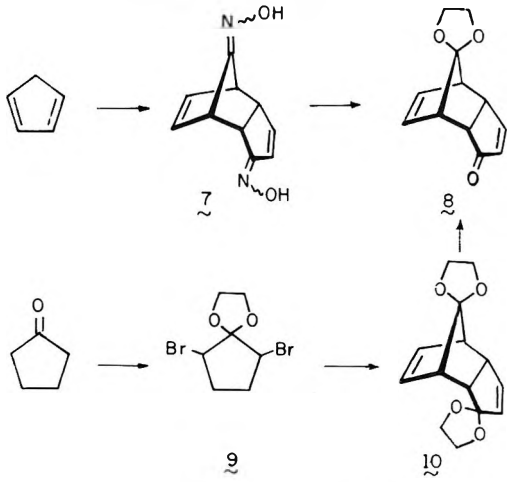
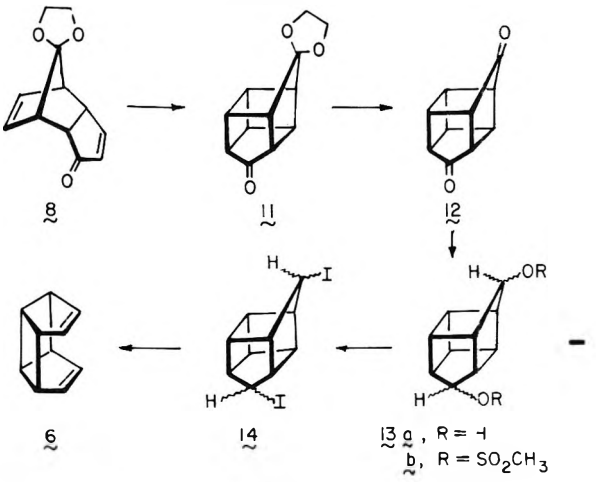
Scheme I



Scheme II



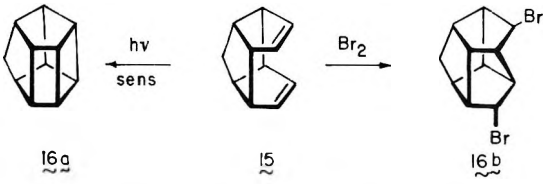
clopentadiene,[17] nitrosation of which provided dioxime **7**.[18] Through sequential transoximation with levulinic acid[19] and selective ketalization with ethylene glycol in benzene containing *p*-toluenesulfonic acid,[20] this dioxime was efficiently converted to **8**. Although this sequence is quite satisfactory for either small- or large-scale preparations of **8**, there remain undesirable economic and technical problems in the handling of bulk quantities of levulinic acid. These drawbacks were totally eliminated through use of cyclopentanone as starting material. Conversion to its ethylene ketal[21] followed by dibromination with elemental bromine in dioxane[20b] gave **9**. To achieve maximum yields in the latter step, **9** should be isolated immediately without unnecessary heating during solvent removal and used directly. When left at room temperature for any length of time, the dibromo ketal is transformed to a dense black oil. Dehydrobromination of **9** and in situ dimerization were achieved through the use of refluxing sodium methoxide in methanol,[20b] or preferably sodium or potassium *tert*-butoxide in *tert*-butyl alcohol. Partial hydrolysis of **10** to **8** could be reproducibly achieved in 95% yield by stirring with hydrochloric acid in tetrahydrofuran at room temperature for 2 h. Extension of the reaction time to 4–5 h invariably caused drastic reductions in yield.

Upon irradiation of **8** in ether through Pyrex with a Hanovia 450-W lamp, photoclosure to **11** was routinely realized in 95% yield. Although the subsequent hydrolysis of **11** to **12** is somewhat capricious and requires careful attention to detail, this approach to **12** is vastly superior to that involving direct photocyclization of dicyclopentadienone,[22] since no photochemical side reactions compete. Lithium aluminum hydride reduction of **12**, treatment of diol mixture **13a** with sulfene,[23] and S_N2 displacement with sodium iodide in anhydrous hexamethylphosphoramide afforded the nicely crystalline **14** as a mixture of epimers (Scheme II).

Initially, the conversion of diiodide **14** to hypostrophene was effected with sodium–potassium alloy in anhydrous tetrahydrofuran at room temperature (54% yield). To remove the last traces of solvent and some polymerization product, the impure **6** was generally sublimed. But contamination with a saturated hydrocarbon byproduct of comparable volatility persisted. These complications do not arise if ether is originally employed as solvent. Under these conditions, chromatography on silica gel (unfeasible earlier) suffices to provide pure hypostrophene (61%). Other methods such as those involving sodium naphthalenide or sodium phenanthrenide suffer from the problem of ultimate separation of volatile **6** from aromatic compounds and are substantially less desirable.

These procedures therefore permit the ready production of hypostrophene in 14.6% overall yield from cyclopentadiene or, more impressively, in 21.6% yield from cyclopentanone.

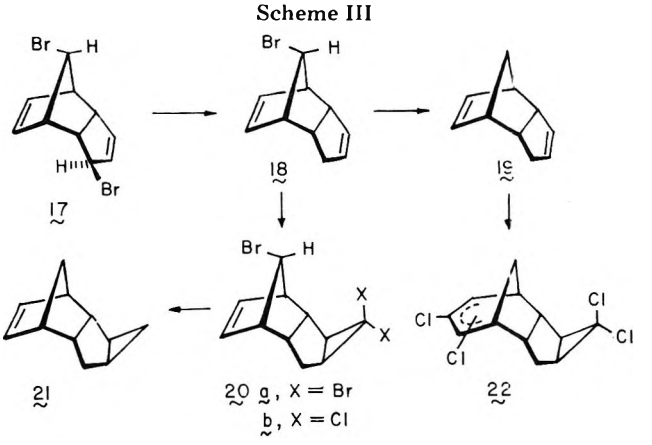
Chemical Consequences of Through-Bond Interaction. To assess in reasonably systematic fashion the degree of control that high-lying σ orbitals can exert upon chemical reactivity, comparisons with one or more compounds lacking through-bond interaction are warranted. For the present purposes, homohypostrophene (**15**) is considered particularly attractive because of its close structural similarities to **6**. Although photoelectron spectroscopic analysis of **15** has yet to be reported, this diene lacks laterally fused cyclobutane rings and probably is endowed with normal orbital ordering. That through-space interaction does dominate in **15** is suggested by its closure to homopentaprismane (**16a**) upon ultraviolet



irradiation in the presence of xanthone or acetone.[24] A further chemical test in support of this conclusion is found in the bromination of **15**, which proceeds straightforwardly by 1,4 addition to give exclusively **16b**.[25,26]

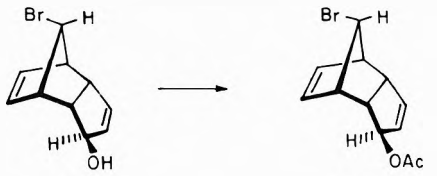
Reaction of **6** at 0 °C in carbon tetrachloride with 1 equiv of bromine gave a single oily dibromide (**17**) in excellent yield. The ^1H NMR spectrum of **17** displays four olefinic protons, thereby ruling out the operation of simple transannular chemistry as exhibited by **15**. Because reduction of **17** with lithium aluminum hydride afforded an isomerically pure monobromide, it became immediately apparent that its halogens are situated in differing chemical environments. The finding that further dehalogenation with sodium in liquid ammonia furnished *endo*-dicyclopentadiene (**19**) implicated the prior formation of **17** and **18** (Scheme III). The syn stereochemical assignment to the 8-bromo substituent in these

Scheme III



molecules is founded upon the selective reactivity of **18** toward dihalocarbenes generated under phase-transfer conditions[28] and upon mechanistic reasoning (vide infra).[29] The steric shielding which arises with this substitution plan causes **18** to be subject only to monoaddition with formation of **20a** and **20b** under conditions where parent hydrocarbon **19** undergoes reaction at both olefinic sites to give **22.** Upon reductive dehalogenation, **20a** and **20b** were transformed to the known hydrocarbon **21.**[30]

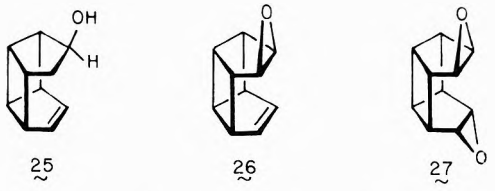
When hypostrophene was treated with *N*-bromosuccinimide in wet dimethyl sulfoxide, a reagent known to lead regio- and stereospecifically to bromohydrins[31a] with skeletal rearrangement occurring only infrequently,[31b] there was isolated only the extensively isomerized bromo alcohol **23.** The identity of **23** is based upon its formation by hydrolysis of **17** and the spectral properties of its more stable acetate derivative **24** (see



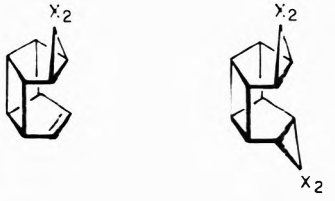
23 24

Experimental Section). These results are taken as an indication that hypostrophene possesses a powerful latent drive for rearrangment that is accompanied by strain release and made possible by its electron-rich lateral bonds.

Nonetheless, reagents such as 9-borabicyclononane (9-BBN),[32] *m*-chloroperbenzoic acid, dibromocarbene, and iodomethylzinc iodide engage **6** in chemical reaction (exo attack only) without inducing skeletal isomerization. With 9-BBN, the multiplicity of addition could be controlled to give alcohol **25** in >70% isolated yield. We have directed efforts toward the maximization of monoaddition in all instances, but the 70+% limit has been repeatedly realized under individually tailored experimental circumstances. For example, *m*-chloroperbenzoic acid in chloroform at 0 °C provided monoepoxide **26** (73%) and diepoxide **27** (15%). With potassium *tert*-butoxide and bromoform in pentane at −30 °C, there was isolated 77% of **28a** and 15% of **29a.** Simmons–Smith cyclopropanation



25 26 27

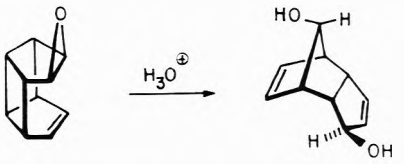


28 a, X = Br
b, X = H

29 a, X = Br
b, X = H

similarly gave a mixture of **28b** and **29b,** and the need for preparative VPC separation substantially lowered the isolated yields in this case. Reductive debromination[33] of **28a** is the preferred route to **28b.**

No rearrangement products are formed in the above reactions due to the absence of mechanistic requirements that cationic intermediates intervene. When this is purposefully undertaken as, for example, when **26** is dissolved in 10% aqueous perchloric acid at room temperature, rapid conversion to the known 1-*exo*-8-*syn*-diol **30** does occur.



26 30

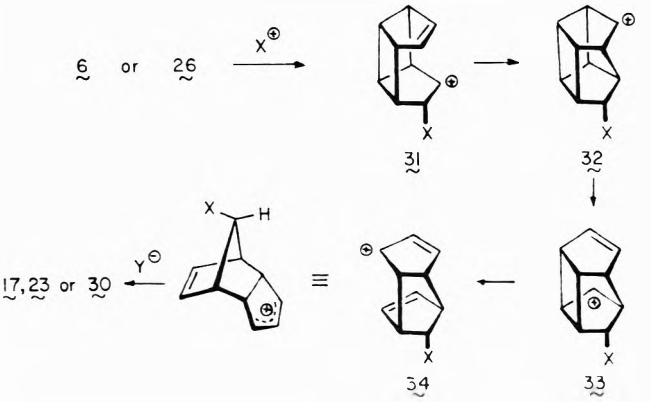
Discussion

An intriguing feature of the conversion of hypostrophene to **17** and **23** is the involvement of *eight* of this hydrocarbon's ten constituent carbon atoms in the skeletal rearrangement. We believe that electrophilic attack begins with exo approach to generate **31.** This intermediate subsequently experiences transannular bonding with the normal kinetic preference for 5-ring closure (Scheme IV) to deliver **32.** Two sequential cyclobutane bond cleavages follow. The first phase leading to **33** is quite likely facilitated by the electron-rich nature of the lateral bond and controlled by strain release since the new cationic center does not appear to be particularly stabilized relative to that in **32.** The energetic value of the second phase which gives rise to **34** probably lies chiefly in the development of allylic resonance, although a further diminution in strain also obtains. As a direct consequence of the prevailing symmetry in **34,** nucleophilic capture can take place with equal probability at either allylic terminus.

The behavior of epoxide **26** in acidic solution is entirely comparable. Here, electrophilic ring opening leads to **31** (X = OH) which then proceeds to **30** in the predescribed manner.

We have been singularly unsuccessful in our attempts to intercept such hypostrophene rearrangements even with most reactive uniparticulate electrophiles[34] such as TCNE and CSI. Due to the geometric limits imposed upon intramolecular charge annihilation when uniparticulate reagents are involved, only the capture of **31** and **33** becomes feasible under such circumstances. However, tarry polymeric substances which defied characterization were produced with CSI under the various conditions examined. TCNE proved unreactive. It is, therefore, perhaps more reasonable to view the conversion of **31** to **34** as a concerted electronic reorganization, although we recognize that this hypothesis is based upon negative rather than positive evidence. In this interpretation, the synchronous flow of electron density which undulates between the two "wafered" cyclopentane rings such that 80% of the carbon atoms experience rehybridization can be viewed as the result of the extensive $\sigma\pi$ orbital mixing which prevails. Certainly, if any barriers to bond making and bond breaking do exist on this energy profile, their magnitudes have been greatly reduced as compared to the situation in **15** and other structurally related molecules.

Scheme IV



Experimental Section

Melting points are uncorrected. Proton magnetic resonance spectra were obtained on Varian T-60A and HA-100 spectrometers; apparent splittings are given in all cases. Infrared spectra were obtained with Perkin-Elmer Model 137 and 467 spectrometers, whereas mass spectra were measured with an AEI-MS9 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

***endo*-Dicyclopentadienone.** A substantial quantity of bisoxime **7** was prepared in 77% yield by the method of Doering and DePuy.[18] The crude solid obtained by Soxhlet extraction of the reaction mixture was used without further purification. Its infrared spectrum was identical with that reported.

A mixture of 20 g (105 mmol) of bisoxime **7** in 480 mL of freshly distilled levulinic acid and 54 mL of hydrochloric acid was stirred at room temperature for 3 h during which time the solids dissolved. The orange solution was heated on a steam bath for 3 h, cooled, diluted with 1000 mL of water, and extracted with four portions of methylene chloride totalling 2000 mL. The combined organic layers were carefully neutralized with saturated sodium bicarbonate solution, followed by washing with 100 mL of 20% sodium hydroxide solution and finally with water until color was no longer extracted. The dried solution was filtered and evaporated to leave a yellow solid which was purified by column chromatography on neutral alumina (benzene elution). There was isolated 13.13 g (78%) of dicyclopentadienone as off-white crystals whose spectral properties proved identical with the reported data.[18]

***endo*-Dicyclopentadienone 8-Ethylene Ketal (8). A. Selective Ketalization of *endo*-Dicyclopentadienone.** A solution of 5.10 g (31.8 mmol) of *endo*-dicyclopentadienone, 3.95 g (63.7 mmol) of ethylene glycol, and 100 mg of *p*-toluenesulfonic acid in 50 mL of benzene was heated under reflux while water was azeotropically removed in a Dean–Stark trap. After 22 h the mixture was cooled, extracted with equal volumes of saturated sodium bicarbonate solution and water, and dried. Elution of the filtrate through 10 g of neutral alumina and evaporation of solvent gave 5.15 g (81%) of **8** as a white solid. This material could be recrystallized from carbon tetrachloride to a melting point of 94–95 °C (lit.[20a] mp 94–95 °C), or used without further purification.

B. Partial Hydrolysis of 10. Cyclopentanone ethylene ketal (87% yield) and 2,5-dibromocyclopentanone ethylene ketal (96% yield) were prepared according to literature procedures.[20b,21]

To 2000 mL of dry *tert*-butyl alcohol was added 141 g (3.6 g-atom) of potassium metal portionwise during 1 h under a nitrogen atmosphere with mechanical stirring. The mixture was gently refluxed to achieve reaction of the last amounts of potassium. To this potassium *tert*-butoxide solution was added 281.28 g (0.98 mol) of **9** dropwise under nitrogen. The resultant black mixture was heated gently for 12 h and diluted with 2000 mL of water. The *tert*-butyl alcohol was removed under reduced pressure and the black aqueous mixture was diluted to 5000 mL and extracted continuously with diethyl ether to give 104 g (86%) of **10** as light yellow crystals. Recrystallization from ether gave colorless crystals: mp 91–92 °C (lit.[20b] mp 92 °C); NMR 6.10–6.33 δ_{Me_4Si} ($CDCl_3$) (m, 1), 5.5–5.97 (m, 3), 3.82–4.07 (m, 8), 3.33–3.62 (m, 1), and 2.58–3.05 (m, 3).

A solution of 60.8 g (0.245 mol) of **10** in a mixture of 96 mL of concentrated hydrochloric acid and 960 mL of tetrahydrofuran was allowed to stand at room temperature for 2 h and no longer. Water (1 L) was added and the aqueous mixture was neutralized carefully with sodium carbonate. The tetrahydrofuran was removed on a rotary evaporator and the aqueous layer was diluted to 1000 mL, extracted exhaustively with diethyl ether, and dried. Filtration and evaporation gave 49.36 g (100%) of **8** as colorless crystals, mp 94–95 °C.

Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione 6-Ethylene Ketal (11).[20] A solution of 28.6 g (0.14 mol) of **8** in 1500 mL of dry benzene was placed in a large Pyrex vessel and irradiated with a 450-W Hanovia lamp contained in a quartz immersion well equipped with a Pyrex filter for 36 h. Filtration of the resultant yellow solution through 10 g of Florisil removed colored impurities and led to the isolation of 27.0 g (94%) of **11** as a colorless oil. If desired, crystallization could be achieved at −60 °C from diethyl ether.

Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (12). A heterogeneous mixture of 2.39 g (11.7 mmol) of **11**, 110 mL of 10% aqueous sulfuric acid, and 20 mL of tetrahydrofuran was heated at 80–90 °C for 3 h with stirring. After cooling, the mixture was poured onto 100 g of ice and carefully neutralized with solid sodium bicarbonate. The contents of the flask was diluted to 700 mL with water and extracted continuously with methylene chloride. Evaporation of the organic phase gave 1.71 g of orange oil, chromatography of which on silica gel (elution with benzene/ethyl acetate, 4:1) gave **12** as colorless crystals (1.42 g, 76%). The physical and spectral properties of **12** coincided with those described in the literature.[22]

This diketone, on standing open to the air, gradually forms a hydrate which appears as a white powder.

Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-diol (13a). To a stirred suspension of 9.9 g (0.26 mol) of lithium aluminum hydride in 300 mL of dry tetrahydrofuran under nitrogen was added dropwise a solution of 20.7 g (0.13 mol) of **12** in 400 mL of dry tetrahydrofuran. The resultant mixture was heated under reflux for 24 h, cooled, and treated carefully with 10 mL of water, 10 mL of 15% sodium hydroxide solution, and 30 mL of water. The mixture was suction filtered and the solids were leached repeatedly with diethyl ether. The combined organic filtrates were evaporated under reduced pressure to give 19 g (90%) of a pale yellow oil. Recrystallization from benzene gave 6.84 g of colorless crystals: mp 185–197 °C (mixture of epimers); NMR δ_{Me_4Si} ($CDCl_3$) 2.10 (br s, 2), 2.68 (m, 4), 2.88 (m, 4), and singlets at 3.98, 4.20, and 4.36 (total 2 H) (the three methine signals appeared in the ratio 5:16:4); IR ν_{max} (neat) 3320 cm^{-1}.

6,10-Bis(methanesulfonyloxy)pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]-decane (13b). To a solution of 1.61 g (9.8 mmol) of **13a** in 200 mL of methylene chloride at 0 °C was added 2.52 g (22 mmol) of triethylamine under nitrogen. Methanesulfonyl chloride (3.0 g, 29.7 mmol) was added dropwise over 30 min at 0 °C and the resultant clear solution was maintained at 0 °C for an additional 20 min before being poured into 200 mL of ice water. The aqueous phase was extracted with 100 mL of methylene chloride and the combined organic layers were washed consecutively with cold 5 N hydrochloric acid (200 mL) and saturated sodium bicarbonate solution, prior to drying and evaporation. There was obtained 2.68 g (85%) of a white crystalline solid, recrystallization of which from ethyl acetate gave colorless blades: mp 151.5–153 °C; NMR δ_{Me_4Si} ($CDCl_3$) 2.8 (m, 4), 3.02 (s, 6), 3.2 (m, 4), and singlets at 4.74, 4.90, and 5.04 (total 2 H).

Anal. Calcd for $C_{12}H_{16}O_6S_2$: C, 44.99; H, 5.03; S, 20.02. Found: C, 44.93; H, 5.06; S, 19.81.

6,10-Diiodopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (14). A mixture of 200 mg (0.6 mmol) of dimesylate **13b** and 1.88 g (12.5 mmol) of sodium iodide in 4 mL of anhydrous hexamethylphosphoramide was heated to 130–140 °C under nitrogen for 2 days. The resultant black solid mixture was cooled and treated with 50 mL of water. The suspension was extracted with diethyl ether followed by washing of the combined organic phases with 6 N hydrochloric acid, water, and saturated sodium bicarbonate solution. Drying, filtration, and evaporation left 230 mg of orange oil which solidified on standing. The diiodide was purified by column chromatography on silica gel (pentane elution). The colorless crystals so obtained (216 mg, 90%) were recrystallized from petroleum ether: mp 171–173 °C; NMR δ_{Me_4Si} ($CDCl_3$) 2.44–3.60 (br m, 8) together with singlets at 3.76, 3.88, and 4.02 (total 2 H).

Anal. Calcd for $C_{10}H_{10}I_2$: C, 31.28; H, 2.63. Found: C, 31.56; H, 2.77.

Tetracyclo[5.3.0.0^{2,6}.0^{3,10}]deca-4,8-diene (6). Method A. A dry 250-mL three-neck, round-bottom flask was charged with 2 g (87 mg-atom) of sodium and 2 g (51 mg-atom) of potassium under nitrogen. The flask was evacuated to 0.1 mm and the metals were fused by heating with a Bunsen burner. The flask was permitted to cool and the vacuum was carefully released under nitrogen. The sodium–potassium alloy was treated with 50 mL of dry tetrahydrofuran followed by the dropwise addition of 4.95 g (12.9 mmol) of **14** in 100 mL of the same solvent. The resultant gray suspension was stirred for 12 h and allowed to settle. The supernatant solution was removed by syringe and the flask was rinsed with 25 mL of pentane which was again removed by syringe. The combined organic layers were suction filtered through a pad of Celite to remove inorganic solids and the filtrate was carefully concentrated under reduced pressure (80 mm) at 10 °C to a volume of 25 mL. The dark solution was diluted to 250 mL with water and extracted with three 100-mL portions of pentane. The combined organic extracts were washed several times with water and brine prior to drying. After filtration, the volume of solution was reduced to 10 mL as before and the solution was placed in a sublimator where the remainder of the solvent was removed under vacuum. Sublimation of hypostrophene from the resultant orange oil was achieved at 25 °C and 0.1 mm with the use of a dry ice cooled cold finger to give 890 mg (54%) of **6** as pungent colorless plates. The spectra of this hydrocarbon were identical with those described earlier.[9]

Method B. A dry 1-L round-bottom flask was charged with 8.0 g of sodium and 8.0 g of potassium. After evacuation, the alloy was prepared as described above. After cooling, anhydrous ether (200 mL) was added under a nitrogen atmosphere. The resulting mixture was

stirred magnetically. A solution of **14** (20 g) in 400 mL of ether was added dropwise, and stirring was maintained at room temperature for 15 h. Workup in the predescribed manner (except washing with ether) followed by careful removal of solvent left 5.2 g of a low melting solid which was chromatographed on silica gel (pentane elution). The amount of hypostrophene recovered was 4.1 g (61%).

Bromination of Hypostrophene. To an ice-cold solution of **6** (0.5 g) in 20 mL of carbon tetrachloride was slowly added 0.62 g of bromine with a syringe. Stirring was continued for 30 min prior to washing with water and drying. Removal of the solvent left 1.12 g (95%) of **17** as a pale yellow oil which turned dark green after several hours at room temperature: NMR δ_{Me_4Si} ($CDCl_3$) 5.92 (m, 2), 5.72 (m, 2), 3.92 (m, 1), and 3.70–3.0 (m, 4); *m/e* calcd 287.9150, found 287.9156.

***syn*-3-Bromo-*endo*-dicyclopentadiene (18).** A solution of **17** (1.0 g) in 5 mL of anhydrous ether was added dropwise to a stirred suspension of lithium aluminum hydride (0.3 g) at 20 °C, cooled to 0 °C, and treated sequentially with 0.3 mL of water, 0.3 mL of 15% sodium hydroxide solution, and 0.9 mL of water. The precipitated salts were removed by filtration and rinsed well with ether. The filtrate was washed with brine, dried, and evaporated to give 0.57 g (80%) of **18**: NMR δ_{Me_4Si} ($CDCl_3$) 5.93 (m, 2), 5.48 (m, 2), 3.92 (m, 1), 3.42–2.40 (m, 5), and 2.27–1.98 (m, 1); *m/e* calcd 210.0045, found 210.0048.

***endo*-Dicyclopentadiene (19).** To a stirred solution of 0.40 g of sodium in 40 mL of liquid ammonia maintained at −78 °C was added dropwise 900 mg of **18** dissolved in 10 mL of ether. After 30 min, solid ammonium chloride was added to discharge the blue color, the ammonia was allowed to evaporate, water (25 mL) was added, and the product was extracted into ether (3 × 20 mL). The combined organic layers were dried and evaporated to give 510 mg (92%) of hydrocarbon **19**, the spectral properties of which were identical with those of an authentic sample.

Dibromocarbene Addition to 18. To a solution containing 250 mg of **18**, 50 mg of triethylbenzylammonium bromide, 7.6 g of bromoform, and 3 mL of benzene was added 1.6 mL of 50% sodium hydroxide solution and the mixture was stirred at room temperature for 48 h. Water (10 mL) was added and a small amount of tarry solid was removed by filtration. The layers were separated and the aqueous phase was extracted with chloroform (3 × 25 mL). The combined organic solutions were washed with brine, dried, and evaporated. There was obtained 0.4 g of an oil which solidified on overnight storage in a refrigerator. Two recrystallizations from ethanol afforded 250 mg (55%) of pure **20a**: mp 105–106 °C; NMR δ_{Me_4Si} ($CDCl_3$) 6.17 (m, 2), 3.90 (m, 1), 3.30–3.10 (m, 1), 3.10–2.28 (m, 3), and 2.25–1.57 (m, 4).

Anal. Calcd for $C_{11}H_{11}Br_3$: C, 34.50; H, 2.90. Found: C, 34.84; H, 3.05.

Dichlorocarbene Addition to 18. The identical procedure was followed, except for substitution of bromoform by chloroform. There was obtained a 71% yield of **20b**, mp 78–79 °C, after two recrystallizations from ethanol. The ^1H NMR spectrum of **20b** was similar in many respects to that of **20a**.

Reduction of 20a. A solution of **20a** (200 mg) in 3 mL of ether was added dropwise to a solution of sodium metal (300 mg) in liquid ammonia (50 mL) maintained at −70 °C. After 30 min, the excess sodium was destroyed by addition of solid ammonium chloride. The ammonia was allowed to evaporate, water was carefully added, and the aqueous mixture was extracted with ether (3 × 25 mL). The combined organic layers were dried and carefully evaporated to leave 70 mg (70%) of **21**: NMR δ_{Me_4Si} ($CDCl_3$) 6.15 (m, 2), 3.0–2.15 (m, 4), 1.84–0.71 (m, 6), 0.61–0.31 (m, 1), and 0.19 to −0.42 (m, 1).[29]

Dichlorocarbene Addition to 19. A mixture of *endo*-dicyclopentadiene (0.70 g), triethylbenzylammonium bromide (50 mg), and chloroform (5 mL) was treated with 3.5 mL of 50% sodium hydroxide solution and stirred at room temperature for 60 h. Workup in the predescribed fashion furnished 1.0 g of **22**: NMR δ_{Me_4Si} ($CDCl_3$) 6.04 (m, 1), 4.42 (m, 1), and 3.05–1.40 (m, 10); *m/e* calcd 295.9693, found 295.9696.

***syn*-8-Bromo-*exo*-1-hydroxy-*endo*-dicyclopentadiene (23). A. By Rearrangement of Hypostrophene.** An ice-cold solution of hypostrophene (100 mg) in 1 mL of dimethyl sulfoxide was treated with 0.2 mL of water and 140 mg of *N*-bromosuccinimide and stirred at 0 °C for 2 h. Saturated sodium bicarbonate solution (20 mL) was added, the mixture was extracted with ether (3 × 20 mL), and the combined organic layers were washed with brine and dried. Evaporation of solvent left 130 mg (74%) of **23** as a colorless oil: NMR δ_{Me_4Si} ($CDCl_3$) 5.90 (m, 2), 5.70 (m, 2), 4.09 (m, 1), 3.95 (m, 1), 3.55–3.20 (m, 2), 3.20–2.95 (m, 1), 2.68–2.45 (m, 1), and 2.40 (br s, 1).

The bromo alcohol was converted to its crystalline acetate **24**, mp 90–91 °C (from pentane–ether, 9:1), for further characterization: NMR δ_{Me_4Si} ($CDCl_3$) 6.20–5.55 (m, 4), 4.95 (m, 1), 3.98 (m, 1), 3.60–3.25 (m, 2), 3.25–3.0 (m, 1), 2.60–2.45 (m, 1), and 2.02 (s, 3).

Anal. Calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87. Found: C, 53.61; H, 5.03.

B. Hydrolysis of 17. A mixture of **17** (500 mg), water (6 mL), acetone (12 mL), and calcium carbonate (500 mg) was stirred at 20 °C for 24 h. The acetone was removed under reduced pressure, the residue was diluted with water and extracted with ether (3 × 25 mL), and the combined organic layers were washed with brine and dried. After solvent removal, there remained 350 mg (80%) of **23** which also was directly converted to its acetate, mp 90–91 °C.

***exo*-Tetracyclo[5.3.0.$0^{2,6}$.$0^{3,10}$]dec-4-en-8-ol (25).** A solution of 2.6 g (20 mmol) of **6** in 40 mL of dry tetrahydrofuran was cooled to 0 °C under nitrogen and 9-borabicyclononane in tetrahydrofuran solution (0.5 M, 40 mL, 20 mmol) was added dropwise during 2 h. The resultant mixture was allowed to warm to ambient temperature during 1.5 h and cooled again to 0 °C. Sodium hydroxide solution (15%, 10 mL) was added, followed by 8 mL of 30% hydrogen peroxide. This mixture was stirred for 8 h prior to saturation with potassium carbonate and separation of the layers. The aqueous phase was extracted with 100 mL of ether and the combined organic phases were dried. Filtration and solvent evaporation gave a large quantity of yellow oil which was chromatographed on Florisil (elution with ligroin–ether). Recovered hypostrophone amounted to 0.72 g while later fractions yielded 1.58 g (73%) of exo alcohol **25** as a low-melting, semicrystalline material. Purification could be achieved by gas chromatography on a 6 ft SE-30 column at 110 °C: NMR δ_{Me_4Si} ($CDCl_3$) 6.31 (m, 2), 4.20 (dd, J_{syn} = 7 Hz, 1), 3.32 (m, 5), 2.92 (m, 1), 2.15 (dd, J_{gem} = 15, J_{syn} = 7 Hz, 1), 1.89 (s, 1), and 1.56 (m, 1).

The 3,5-dinitrobenzoate of **25**, prepared by the customary procedure and recrystallized from ether, was obtained as off-white crystals, mp 136–137 °C.

Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.19. Found: C, 59.76; H, 4.20; N, 8.03.

Epoxidation of Hypostrophene. A solution of 890 mg (6.85 mmol) of **6** in 25 mL of chloroform was cooled to 0 °C under nitrogen and a solution of 1.18 g (6.85 mmol) of *m*-chloroperbenzoic acid in 10 mL of chloroform was added dropwise during 30 min. The reaction mixture was allowed to warm to room temperature with stirring for 12 h prior to washing with saturated sodium bicarbonate solution and drying. The solvent was evaporated under reduced pressure and the resultant yellow oil was taken up in pentane and deposited on a Florisil column. Chromatography (elution with pentane) provided 78 mg of recovered hypostrophene, 667 mg of monoepoxide **26**, and 170 mg of bisepoxide **27**. The yield of monoepoxide based on recovered **6** was 73%, while that of **27** was 15%.

The monoepoxide was recrystallized from pentane and obtained as colorless crystals: mp 170 °C dec; NMR δ_{Me_4Si} ($CDCl_3$) 6.14 (s, 2), 2.84–3.44 (br m, 5), 3.36 (s, 2), and 2.64–2.80 (m, 1).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.02; H, 6.99.

The bisepoxide when recrystallized from ether was isolated as colorless needles which sublimed slowly above 150 °C and decomposed above 200 °C; NMR δ_{Me_4Si} ($CDCl_3$) 3.51 (s, 4), 3.08 (m, 4), and 2.56 (m, 2).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 73.80; H, 6.25.

9,9-Dibromopentacyclo[5.4.0.$0^{2,6}$.$0^{3,11}$.$0^{8,10}$]undec-4-ene (28a). A solution of 170 mg (1.31 mmol) of **6** in 5 mL of pentane was cooled to −30 °C and 291 mg (2.6 mmol) of potassium *tert*-butoxide (sublimed) was added in one portion. The resultant slurry was treated slowly while magnetically stirred with 329 mg (1.30 mmol) of bromoform in 2 mL of pentane. The ten colored suspension was stirred under nitrogen for 12 h at room temperature prior to addition of 25 mL of pentane and 50 mL of water. The layers were separated and the aqueous phase was further extracted with 10 mL of pentane. The combined pentane extracts were washed once with water and dried. Distillation of the pentane at 60 °C through a short Vigreux column left a colorless solution (5 mL) which deposited colorless crystals upon standing in a freezer overnight. The crystalline precipitate was filtered to give 35.5 mg (15%) of bisadduct **29a**. Recrystallization from hexane gave off-white plates which decomposed between 175 and 205 °C: NMR δ_{Me_4Si} ($CDCl_3$) 3.18 (dd, 4), 2.78 (m, 2), and 2.35 (s, 4).

Anal. Calcd for $C_{12}H_{10}Br_4$: C, 30.41; H, 2.13. Found: C, 30.52; H, 2.20.

The mother liquors were evaporated under reduced pressure to give a yellow oil from which was sublimed 100 mg of hypostrophene [50–60 °C (20 mm)] and finally 126 mg (77%) of **28a** [60 °C (0.05 mm)] as white crystals which turned yellow on standing. Recrystallization from pentane provided large, colorless crystals: mp 79–80 °C; NMR δ_{Me_4Si} ($CDCl_3$) 6.23 (s, 2), 3.10–3.48 (br m, 4), 3.01 (m, 1), 2.76 (m, 1), and 2.03 (s, 2).

Anal. Calcd for $C_{11}H_{10}Br_2$: C, 43.74; H, 3.34. Found: C, 43.84; H, 3.37.

Pentacyclo[5.4.0.0^{2,6}.0^{3,11}.0^{8,10}]undec-4-ene (28b). A. Simmons–Smith Reaction of Hypostrophene. A zinc–silver couple was prepared as follows: a mixture of 2 mg of silver acetate in 1 mL of glacial acetic acid was heated to boiling and 144 mg (2.2 mg-atom) of 30 mesh granulated zinc was added in one portion with stirring under nitrogen. After 30 s, the acetic acid solution was pipetted from the mixture and the couple was washed with 1 mL of fresh acetic acid followed by five 1-mL portions of anhydrous diethyl ether. Finally, 1.5 mL of dry diethyl ether was added as the reaction solvent.

The ether suspension of the gray-brown couple was treated with 100 mg (0.77 mmol) of **6**. While under nitrogen, a solution of 295 mg (1.1 mmol) of diiodomethane in 1.5 mL of ether was added dropwise during 10 min. The mixture was refluxed while the progress of the reaction was followed by gas chromatography. After 88 h, the mixture was cooled to 0 °C and pyridine was added dropwise to precipitate zinc salts. After suction filtration, the clear filtrates were again treated with pyridine until no more precipitate formed. The mixture was filtered and reduced in volume to 1 mL. Preparative gas chromatography on a 2 ft SE-30 column at 65 °C gave three components: 10 mg of recovered hypostrophene, 17 mg (17% yield) of **28b**, and 15 mg (14%) of **29b**. For **28b**: NMR δ_{Me_4Si} ($CDCl_3$) −0.24 (dd, 1), 0.25 (dt, 1), 1.19 (dd, 2), 2.48–3.46 (br m, 6), and 6.28 (br s, 2).

Anal. Calcd for $C_{11}H_{12}$: C, 91.08; H, 8.92. Found: C, 91.48; H, 9.07.

For **29b**: NMR δ_{Me_4Si} ($CDCl_3$) −0.33 (dd, 2), 0.36 (dt, 2), 1.42 (dd, 4), 2.36–2.64 (m, 4).

Anal. Calcd for $C_{12}H_{14}$: C, 91.61; H, 8.39. Found: C, 91.26; H, 8.77.

B. Reductive Debromination of 28a. A solution of 50 mg (0.165 mmol) of **28a** in 1 mL of dry tetrahydrofuran was treated with 50 mg of lithium wire and 0.5 mL of dry *tert*-butyl alcohol portionwise over 30 min. After 1 h, a cloudy precipitate had formed and the lithium was visibly reacting. After an additional 3 h, the mixture was decanted to remove lithium pieces and the solution was diluted with 25 mL of water. The aqueous mixture was extracted with two 25-mL portions of diethyl ether followed by washing of the combined organic layers with water and drying. The mixture was filtered and concentrated by distillation through a short Vigreux column (60 °C bath) to a volume of 1 mL. Preparative gas chromatography on a 2 ft SE-30 column at 65 °C gave 18 mg (76%) of a colorless oil whose ^{1}H NMR spectrum was identical with that of **28b** prepared in part A.

***exo*-1,*syn*-8-Dihydroxy-*endo*-dicyclopentadiene (30).** Epoxide **26** (60 mg) was added to 5.0 mL of 10% perchloric acid. The flask was stoppered and the mixture shaken at room temperature for 3 h. Neutralization was effected with sodium bicarbonate solution. After dilution with brine (150 mL), the solution was continuously extracted with methylene chloride for 2 days. The extract was dried and concentrated to leave 50 mg (76%) of **30** which was directly acetylated (90%) to facilitate handling: NMR δ_{Me_4Si} ($CDCl_3$) 6.12–5.92 (m, 1), 5.92–5.73 (m, 2), 5.73–5.57 (m, 1), 4.98 (m, 1), 4.58 (m, 1), 3.57–3.18 (m, 2), 3.12–2.95 (m, 1), 2.65–2.47 (m, 1), 2.03 (s, 3), and 1.98 (s, 3). These compounds exhibited spectra identical with those of authentic samples.[35]

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Impact of High-Lying σ Orbitals and Extensive Through-Bond Interaction on Chemical Reactivity. 2. Solvolytic Studies of Hypostrophene Derivatives[1]

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Acetolysis of exo- and *endo*-tetracyclo[5.3.0.0^{2,6}.0^{3,10}]decan-4-yl tosylates (**6b** and **8b**) in buffered HOAc at 71 °C produced **16b** (together with 2% of **6c** in the endo case), but at rates estimated to differ by a factor of 170 (with **6b** faster). Comparable solvolysis of the unsaturated exo tosylate **3b** (at 25.9 °C) led rapidly to **18b** (50%), **19a** (5%), and **19b** (45%), a product distribution quite unlike that obtained from its endo epimer **5b** (**18b** accompanied by some polymer formation). These findings demonstrate that the frequently observed ability of a proximate double bond to engage in transannular participation has been overridden by lateral σ-bond participation. The kinetic and product data suggest that the first cation emanating from **5b** is classical, while that from **3b** is generated with anchimeric assistance and characterized by σ delocalization. Whereas acetolysis (71 °C) of *exo*-cyclopropyl derivative **10b** returned only **20a**, its endo counterpart **15b** gave a complex acetate product mixture at a rate approximately 440 times slower. The involvement of neighboring-group participation could again be implicated for **10b**, since interaction of the cationic center with the cyclopropane ring is effectively repressed. The rate constants and product distributions provide convincing demonstration of the effectiveness with which such anchimeric assistance can accelerate and control the ultimate outcome of cationic rearrangements.

Interest in hypostrophene (tetracyclo[5.3.0.0.^{2,6}.0^{3,10}]-deca-4,8-diene (**1**))[1-3] derives chiefly from its structural features, including its C_{2v} symmetry, the overriding by through-bond coupling of direct through-space π–π interaction,[4] and its obvious strain energy. The primary determinants of the observed level ordering in **1** are its exceptionally high-

1 **2**

lying lateral σ orbitals and their geometric relationship to the π bonds. Such symmetry-enforced indirect interaction between the double bonds should have significant consequences on chemical reactivity. This conclusion has received qualitative support from the response of **1** to attack by electrophilic reagents.[1,5]

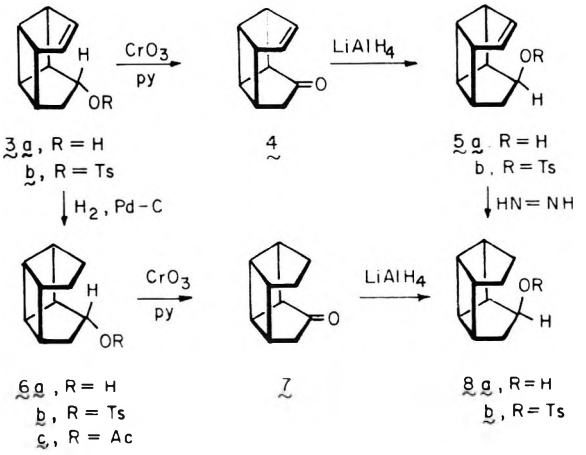
Hoffmann, Mollère, and Heilbronner have previously presented arguments supporting the notion that the exceptional unreactivity of 7-norbornyl cation precursors (**2**) is due not to the change in angle strain accompanying their ionization,[6] but to destabilization brought on by the inability of proper ribbon orbitals to interact suitably with the carbonium ion center.[7] This lack of interaction causes **2** to be less stable and more difficult to generate than it should otherwise be. At issue is whether similar phenomena would be observed in carbonium ions derived from **1** and allied structures.

The recent availability of efficient routes to **1** and the knowledge that carbocations are particularly sensitive to prevailing orbital interactions prompted a detailed kinetic study of the solvolytic behavior of a number of hypostrophene derivatives. In particular, a series of *exo*- and *endo*-*p*-toluenesulfonate esters have been prepared in which the transannular units positioned in close proximity to the leaving group vary from saturated ethano through etheno to edge cyclopropano. Their acetolysis forms the subject of this report.

Results

Synthesis. Oxidation of *exo*-alcohol **3a**, the monohydroboration product of hypostrophene,[1] gave ketone **4** which was reduced stereospecifically to **5a** with lithium aluminum hydride (Scheme I). Careful catalytic hydrogenation of **3a** led

Scheme I



to **6a** and subsequently to **8a** without complication. Diimide reduction of **5a** likewise provided **8a**.

Although the available **9**[1] could be cleanly converted to **10a** with 9-BBN, the somewhat limited accessibility of this hydrocarbon led us to develop a preferred route beginning with acetate **11**. Dichlorocarbene addition to **11** was conveniently achieved under phase-transfer conditions. The resulting adduct **12** was reduced sequentially with lithium aluminum hydride and sodium in liquid ammonia in good overall yield (Scheme II). Inversion of hydroxyl stereochemistry to provide **15a** was again achieved via an oxidation–reduction sequence.

Solvolysis Kinetics. Acetolyses of the *endo*-tosylates **5b**, **8b**, and **15b** were examined kinetically in buffered acetic acid (0.03 M in NaOAc) through use of the standard ampule technique and classical titrimetry. The method previously described by Wiberg and Hess[8] was utilized with *exo*-tosylates **6b** and **10b**. We highly recommend this technique in those situations where solvolysis is quite rapid or when the ionization process is complicated by substantial levels of early internal return. Its chief disadvantage, however, is the rather larger amounts of tosylate (~200 mg) required for a single run. As described in the Experimental Section, a procedural modification has been developed in the course of our study of **3b** which has proven reliable at the 20-mg level.

Due to formation of extensive amounts of less reactive isomeric tosylates arising from internal recapture of *p*-toluenesulfonate anion, reliable instantaneous rate constants

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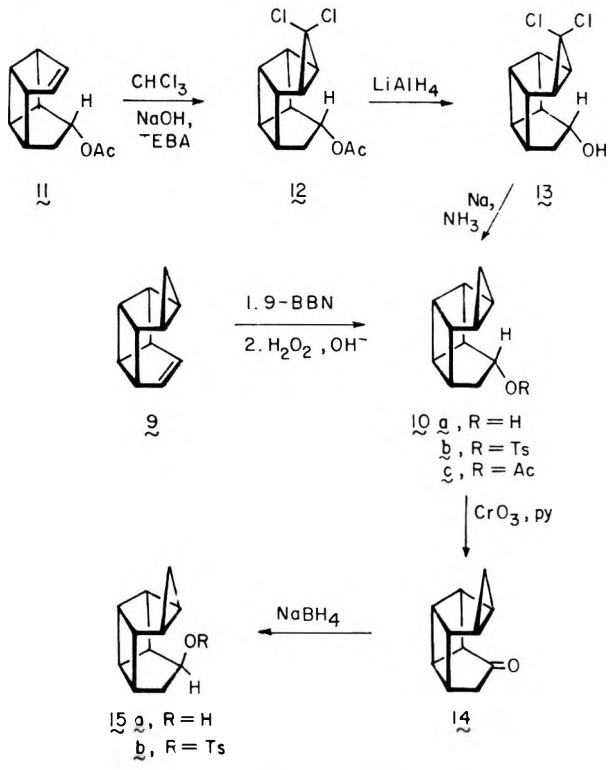
Table I. Rates of Tosylate Solvolysis in Buffered Acetic Acid

Compd	Registry no.	T, °C	k, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	k_{rel} (25.9 °C)
3b	65071-87-6	25.9	4.19×10^{-4}			1000
5b	65137-10-2	55.2	2.12×10^{-4}	21.2 ± 1.0	−11 ± 3	20
		51.1	1.46×10^{-4}			
		44.6	7.02×10^{-5}			
		25.9[a]	8.2×10^{-6}			
6b	65071-88-7	25.9	1.06×10^{-5}			25
8b	65137-11-3	83.6	1.42×10^{-4}	20.7 ± 0.9	−8.5 ± 2.5	1
		77.1	8.47×10^{-5}			
		71.0	4.62×10^{-5}			
		25.9[a]	4.3×10^{-7}			
10b	65071-89-8	25.9	1.71×10^{-5}			41
15b	65137-12-4	83.6	2.33×10^{-4}	23.8 ± 0.5	−8.7 ± 1.3	0.6
		77.1	1.19×10^{-4}			
		71.0	6.52×10^{-5}			
		25.9[a]	2.7×10^{-7}			

[a] Extrapolated values based on the activation parameters.

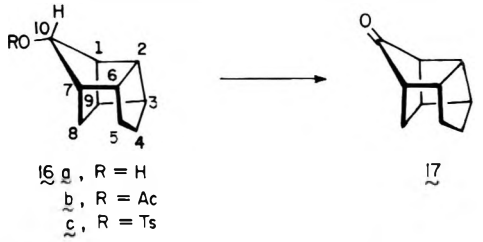
Scheme II



for **6b** and **10b** could be obtained only through the first 5− of reaction. For **3b**, the usable range was extendable to 20% conversion to products. Under the conditions employed, the internal return products were determined to be relatively inert. The rate constants given in Table I for these tosylates are therefore the k's for acetate formation only. In particular, they are believed to exclude any significant contributions from secondary acetolysis. The remaining three substrates underwent solvolysis according to simple first-order kinetics.

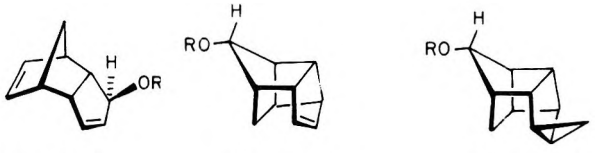
The kinetic data, together with relative rate factors and derived activation parameters (where assessable), are summarized in Table I.

Product Analysis. Upon preparative scale acetolysis at 71 °C, *endo*-tetracyclo[5.3.0.$0^{2,6}$.$0^{3,10}$]decan-4-yl tosylate (**8b**) was converted to a mixture of **16b** (98%) and **6c** (2%). Comparable treatment of the corresponding exo isomer (**6b**) led exclusively to **16b**. Upon lowering the reaction temperature for **6b** to 25.9 °C, the liberation of *p*-toluenesulfonate anion stopped after 15% acetolysis. The product mixture consisted of rearranged tosylate **16c** (85%) and the structurally related acetate **16b**. The structural assignment to **16b** and **16c** is based upon their rather characteristic ^{1}H NMR spectra (e.g., $J_{1,10} = J_{7,10} = 1.5$ Hz), lithium aluminum hydride reduction of **16b** to alcohol **16a**, and Eu(fod)$_3$ induced shifting of the latter. As expected of the *anti*-hydroxyl stereochemistry, the H_1, H_7, *exo*-H_8, H_9, and H_{10} protons in **16a** experienced the greatest



downfield shifting. Also clearly revealed was the geminal coupling of *exo*-H_6 with *endo*-H_8, as well as its vicinal coupling to H_7 and H_9 in accordance with dihedral angle estimates gained from molecular models. Additionally, Collins oxidation of **16a** gave ketone **17** whose intense paired carbonyl absorptions at 1780 and 1765 cm^{-1} compare closely to those of 7-norbornanone (1778 and 1740 cm^{-1}).[9]

The acetolysis of **5b** at 44.5 °C gave **18b** along with 30% polymer. The solvolytic reaction of unsaturated exo isomer **3b** (conducted at 25.9 °C) also led to **18b** (50%), but produced significant amounts of **19a** (5%) and **19b** (45%) as well. That



18b has the designated doubly unsaturated tricyclic structure is based upon its spectral parameters and independent synthesis by acetylation of the known alcohol **18a**.[10] One key feature of the ^{1}H NMR spectra of **19a** and **19b** is the clean narrow triplet (J = 1.5 Hz) which arises from the proton on carbon bonded to oxygen. That this multiplicity is again characteristic of a 7-norbornyl type proton was established by catalytic hydrogenation of **19b** to **16c**. Also, heating of **19b** in buffered acetic acid at 70 °C for 41 h returned exclusively **19a**.

Whereas the acetolysis (71 °C) of **10b** occurred with clean conversion to **20a**, its endo counterpart **15b** gave a more complex distribution of products under identical conditions. Thus, **10c** (8%) and three unsaturated acetates of still unes-

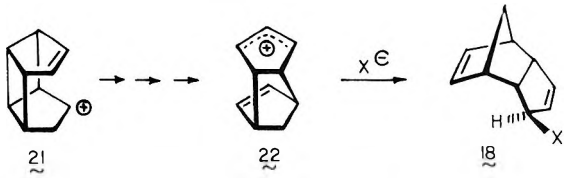
tablished structure (27, 20, and 5%) were isolated in addition to **20a** (40%). The great similarity of the downfield sector of the ^{1}H NMR spectrum of **20a** to those of **16b** and **19a** was taken as evidence that a comparable skeletal rearrangement had taken place.

Discussion

Evidence has been accumulated in the foregoing experiments that the various exo-substituted hypostrophene derivatives are characterized by enhanced solvolytic reactivity. Direct comparison of the apparent acetolysis rate constants given in Table I provides the following exo/endo rate ratios: unsaturated **3b/5b** = 51; saturated **6b/8b** = 25; and cyclopropanated **10b/15b** = 63 (all at 25.9 °C). Suitable control experiments conducted on **6b** and **10b** revealed internal return to be an important feature of their solvolytic chemistry. In contrast, their endo counterparts were not seen to rearrange to isomeric tosylates. In view of the typical product distributions which show **16c** and **20b** to be formed at least six times faster than the acetate products, the true rates of ionization for **6b** and **10b** ($k_{ion} = k_{solv} + k_{int\ ret}$) must in reality be some seven times larger than determined experimentally or 74×10^{-6} and 120×10^{-6}, respectively. If internal return to the starting tosylates is neglected, as it must be under the present circumstances, these *exo*-sulfonate esters are seen to exhibit substantial kinetic enhancement to ionization (170 and 440) relative to the endo-saturated and cyclopropanated derivatives.

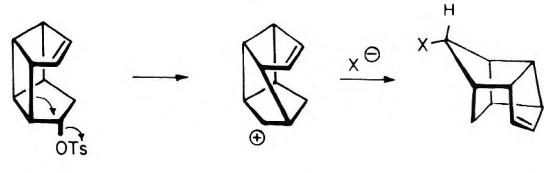
The behavior of **3b** in buffered acetic acid is such that internal return with skeletal rearrangement was again prominent, as reflected in the isolation of **19b** (45%) at 25.9 °C. But this tosylate is also the most reactive of the entire series and the true magnitude of k_{ion} was more difficult to establish conclusively in this instance. Notwithstanding, it is clear that acetolysis of the exo isomers is greatly accelerated by neighboring-group participation, or the endo isomers are unexpectedly slow. The former explanation seems the more reasonable to us, and the ensuing discussion makes clearer our reasons for this choice.

Observations made in earlier work[1] suggest that should **3b** or **5b** experience simple S_N1 ionization to cation **21**, there can

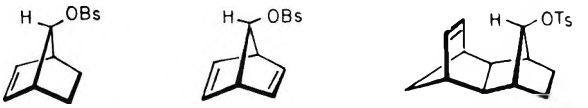


21 22 18

be expected to follow a rapid energy-releasing cascade to the substantially less strained *endo*-dicyclopentadienyl framework **22** and eventual nucleophilic capture of the latter to give **18**. Convincing evidence that the endo substitution plan in **5b** is conducive to transient generation of **21**, as expected, is found in its isomerization to **18b**. Although the very reactive **3b** experiences partial conversion to **18b** as well, there is also formed significant amounts of **19a** (5%) and **19b** (45%) at 25.9 °C. Consequently, the customarily overwhelming capability of the proximate double bond in **3b** to enter into transannular bonding[1] has been overridden by an alternative electronic realignment involving apparent 1,2-shift of a lateral edge bond. The competitive isomerization to **23** is considered to be



3b 23 19



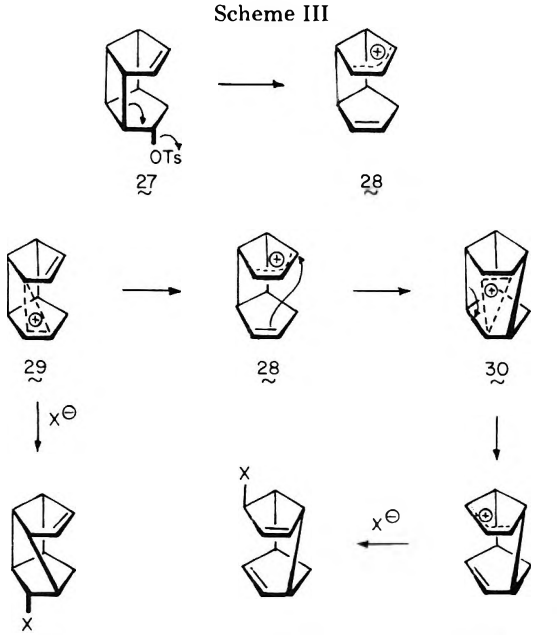
24 25 26

the combined result of an ideal antiplanar stereoelectronic arrangement and the effectiveness with which the electron-rich lateral cyclobutane bond can dissipate positive charge. It is particularly remarkable that the proximate double bond in **3b** does not find it possible to control the ionization in its entirety since one pπ orbital is tightly compressed to the anterior of the departing group. However, the isolation of **19a** and **19b** argues against such domination and provides indication that electronic factors within this hypostrophene derivative differ from that customarily found in such unsaturated molecules as the *anti*-7-norbornenyl (**24**),[11] 7-norbornadienyl (**25**),[12] and octahydrodimethanonaphthyl brosylates (**26**)[13] where through-space interaction is fully operative.

One may now question why the lateral σ bond in **3b** does not enter into electronic reorganization as illustrated in **27** to provide access to the assumedly more thermodynamically stable allylic cation **28** (Scheme III). The reader will undoubtedly be aware of the fact that demonstration of a rate enhancement in solvolysis is good evidence for participation in the transition state, but tells nothing about the structure of the intermediate cation formed. In the present instance, the available data does allow for the possibility that **3b** ionizes with *total* σ anchimeric assistance to produce the nonclassical or rapidly equilibrating ion **29** much in the manner characteristic of 2-norbornyl and related systems. Although bottom-side nucleophilic capture of **29** will lead to **19**, it is not inconceivable that allylic cation **28** can be formed from **29** after the rate determining step and experience subsequent electronic reorganization via **30** and **22** to give products of type **18** (Scheme III). Unfortunately, no labeling scheme will distinguish whether **18** arises from **21** or **29**. The results make it clear, however, that if **29** is the exclusive intermediate of kinetic control its partitioning between direct conversion to **19** and further rearrangement in the **28** → **30** → **22** → **18** manifold is approximately equal.

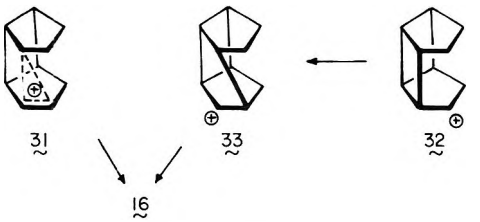
With the exception of 2% inversion of configuration in **8b**, the epimeric saturated tosylates **6b** and **8b** are converted to the same product (**16b**), although at widely differing rates. The formation of **16** further reveals the proclivity of hypo-

Scheme III



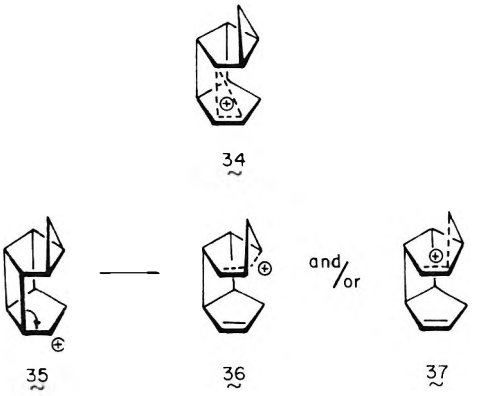
27 28 29 28 30 19 18 22

strophene derivatives for 1,2-migration of an edge cyclobutane bond. If, on the one hand, the position is taken that exo derivative **6b** undergoes acetolysis with anchimeric assistance and conversion to **31**, the rate difference can be attributed in large part to σ-electron delocalization. Alternatively, if it is accepted that the behavior of **6b** is normal and characterized by initial conversion to **33**, the slower rate of ionization ex-



hibited by **8b** must be attributed to steric inhibition of ionization. This analysis would require **6b** to differ phenomenologically from its unsaturated and cyclopropanated analogues (vide infra), a seemingly unwarranted distinction. More importantly, steric factors cannot be chiefly responsible for the slow rate of ionization of **8b**. Molecular models reveal that the pair of endo transannular hydrogens present in **8b** and **15b** and the attendant congestion in the inner sphere of the hypostrophene framework are not greatly different from that found in the endo unsaturated derivative **5b**, due principally to a reduction in conformational flexibility in the latter. Yet, the individual rates exhibited by this trio of *endo*-tosylates differ by only 33-fold, despite the presence of a π bond and cyclopropane ring in close proximity to the ionizing centers in **5b** and **15b** and the well-established capabilities of such groups to inhibit through induction the generation of nearby positive charge.[14] Consideration of the following ratios of acetolysis rate constants ($k_{3b}/k_{6b} = 40$; $k_{3b}/k_{10b} = 25$; $k_{5b}/k_{8b} = 20$; $k_{5b}/k_{15b} = 33$; $k_{8b}/k_{15b} = 1.7$; $k_{6b}/k_{10b} = 0.6$) reveals that *both* the exo-unsaturated and endo-unsaturated tosylates experience ionization some 20–40 times more rapidly than their saturated or cyclopropanated counterparts. In contrast, comparison of the saturated and cyclopropanated compounds lacking unsaturation generates ratios close to unity. Internal return aside, it therefore appears that the cations derived from **3b** and **5b** are stabilized. For the endo example, we attribute this to through-bond stabilization of classical cation **21**. The behavior of the exo system is adequately understood in terms of **29**.

With the exo-cyclopropyl derivative **10b**, efficient conversion to **20a** was noted. This behavior necessarily implicates **34** (or its rapidly equilibrating equivalent) since endo isomer **15b** gives a rather different product profile. The formation of several unsaturated acetates, for example, appears to be related to lateral bond cleavage within classical cation **35** to deliver **36** and/or **37** (this point remains to be unequivocally established). Evidently, the anchimeric assistance in **34** succeeds in repressing this rearrangement with its attendant greater release of strain energy.



The incursion of extensive σ-bond participation during ionization of the *exo*-hypostrophenyl derivatives affords the simplest explanation for both the high reactivities and stereospecific rearrangements described above. Rate-determining involvement of a lateral cyclobutane bond is appropriately in accord with highly effective through-bond coupling known to prevail in this ring system[4,16] and with partial strain relief. Before generalizations can be drawn concerning the extent to which through-bond interaction can be effective in the stabilization of cationic centers, there is a need to consider a variety of other structural types whose electronic structures are reasonably well characterized. The ensuing paper[17] constitutes a step in this direction.

Experimental Section

Melting points are uncorrected. Proton magnetic resonance spectra were obtained on Varian T-60, A-60A, and HA-100 spectrometers; apparent splittings are given in all cases. Infrared spectra were obtained with Perkin-Elmer Model 137 and 467 spectrometers, while mass spectra were measured with an AEI-MS9 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

***exo*-Tetracyclo[5.3.0.0^{2,6}.0^{3,10}]dec-4-en-8-ol Tosylate (3b). General Procedure for Tosylate Formation.** A mixture of the alcohol (3.4 mmol) and *p*-toluenesulfonyl chloride (0.7 g, 3.6 mmol) in 7 mL of dry pyridine was stored in a refrigerator for 24 (exo derivatives) or 72 h (endo derivatives). Ice water (50 mL) was added and after 10 min (certain of the tosylates crystallized within this time) the product was extracted into ether (3 × 50 mL). The combined organic layers were washed with cold 10% hydrochloric acid (3 × 75 mL), saturated sodium bicarbonate solution, and brine prior to drying and solvent evaporation at 0 °C. The residue (oil or crystals) was dissolved in a minimum amount of hexane and stirred with charcoal for 30 min at 20 °C. After filtration and cooling to 0 °C, the tosylates were obtained crystalline and recrystallized to purity from hexane. In the case of **3b**, the white crystalline solid melted at 54–55 °C with decomposition. The individual ^{1}H NMR spectra showed all tosylates to be unrearranged relative to their alcohol precursors.

***endo*-Tetracyclo[5.3.0.0^{2,6}.0^{3,10}]dec-4-en-8-ol (5a).** Dry chromium trioxide (600 mg, 6 mmol) was added to a magnetically stirred solution containing 949 mg (12 mmol) of anhydrous pyridine in 15 mL of freshly distilled methylene chloride. The flask was capped with a Drierite drying tube and the deep burgundy solution was stirred at room temperature for 15 min. A solution of 149 mg (1 mmol) of **3a** in a few milliliters of dry methylene chloride was added in one portion and a tarry black residue immediately formed. After 30 min, the solution was decanted into 10 mL of 5% sodium hydroxide solution and the residue was rinsed with ether. The combined organic layers were washed with two 10-mL portions of 5% sodium hydroxide solution, two 10-mL portions of 5% aqueous hydrochloric acid, 10 mL of saturated sodium bicarbonate, and 10 mL of brine. Drying of the solution, followed by filtration and evaporation of solvent, left 144 mg (97%) of ketone **4** as a pale yellow oil: IR ν_{max} (neat) 1730, 1392, 1343, 1259, 1075, 878, 803, and 739 cm^{-1}; *m/e* calcd 146.0732, found 146.0734.

The ketone was directly dissolved in 10 mL of anhydrous ether and treated with 38 mg (1 mmol) of lithium aluminum hydride followed by gentle refluxing under nitrogen for 1 h. The usual workup[1] provided 160 mg of white crystals which were purified by sublimation [45 °C (0.03 mm)] to give 77 mg (51%) of pure **5a**: IR ν_{max} (KBr) 3370, 1345, 1260, 1110, 1054, 1010, 815, 790, 755, and 733 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 6.65 (dd, 1), 6.23 (dd, 1), 4.34 (m, 1), 3.60–2.80 (br m, 6), 2.52–2.00 (br m, 1), 2.02 (br s, 1), and 1.56 (dd, 1); *m/e* calcd 148.0888, found 148.0891.

The 3,5-dinitrobenzoate was prepared by the customary procedure and isolated as off-white crystals, mp 155–156 °C (from ether), in quantitative yield.

Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18 Found: C, 59.68; H, 4.33; N, 8.12.

Tosylate **5b** was isolated as a colorless crystalline solid, mp 77–77.5 °C.

***exo*-Tetracyclo[5.3.0.0^{2,6}.0^{3,10}]decan-4-ol (6a).** A solution of **3a** (1.40 g) in 75 mL of purified hexane containing 100 mg of 5% palladium on charcoal was hydrogenated at atmospheric pressure (vigorous magnetic stirring) for 40 min. The catalyst was removed by filtration, the solvent was evaporated, and the residue was directly sublimed [55 °C (10 mm)] to give 1.25 g (89%) of **6a** as a waxy colorless solid; NMR

δ_{Me_4Si} ($CDCl_3$) 4.50 (dd, 1), 3.29–2.68 (br m, 6), 2.47 (dd, 1), and 2.00–1.20 (br m, 6); *m/e* calcd 150.1045, found 150.1047.

The 3,5-dinitrobenzoate was obtained in quantitative yield as off-white crystals, mp 135.5–136 °C (from ether).

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.11; H, 4.80; N, 7.98.

Tosylate **6b** was isolated as a colorless crystalline solid, mp 72.5–73 °C.

***endo*-Tetracyclo[5.3.0.0^{2,6}.0^{3,10}]decan-4-ol (8a). A. Diimide Reduction of 5a.** A solution of **5a** (1.8 g, 12.2 mmol) in 150 mL of methanol containing 23.6 g (122 mmol) of potassium azodicarboxylate was cooled to 0 °C and treated dropwise with 20.6 ml of acetic acid during 1 h. Stirring was maintained at 0 °C until the yellow color faded. Then 100 mL of water was added, most of the methanol was evaporated, to give 1.7 g (94%) of **8a**: IR ν_{max} (KBr) 3320, 1110, 1062, 1020, 927, 908, and 890 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 4.32 (m, 1), 3.20–2.48 (br m, 7), and 2.28–1.48 (br m, 6); *m/e* calcd 150.1045, found, 150.1047.

The 3,5-dinitrobenzoate was obtained as off-white plates, mp 148–149 °C (from ether).

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.17; H, 4.79; N, 8.27.

The tosylate **8b** was obtained as a colorless crystalline solid, mp 44.5–45 °C.

B. Oxidation–Reduction of 6a. An 800-mg (5.3 mmol) sample of **6a** was oxidized with 3.2 g (32 mmol) of anhydrous chromium trioxide and 4.96 g of pyridine in 80 mL of methylene chloride as described above. The resulting ketone (0.71 g) was reduced with 0.18 g of lithium aluminum hydride in 15 mL of anhydrous ether and the semicrystalline product was sublimed to give 420 mg of a waxy colorless solid, the spectral features of which proved identical with those of **8a** as detailed above.

***exo*-Pentacyclo[5.4.0.0^{2,6}.0^{3,11}.0^{8,10}]undecan-4-ol (10a).** A solution of 100 mg of **9**[1] in 10 mL of anhydrous tetrahydrofuran was cooled to 0 °C under nitrogen and excess 9-borabicyclononane in tetrahydrofuran solution (10 mL of 0.5 M) was added dropwise during 30 min. Oxidative hydrolysis of this reaction mixture as before[1] gave **10a** in 60% yield. The alcohol was purified by preparative VPC on a 30% SE-30 column at 105 °C: IR ν_{max} (neat) 3380, 1055, 1009, and 900 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 4.69 (dd, 1), 3.24–2.36 (br m, 7), 1.72–1.20 (br m, 4), 0.30 (dt, 1), and −0.25 (dt, 1).

The 3,5-dinitrobenzoate was obtained as off-white clusters, mp 148–149 °C (from ether).

Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.43; H, 4.64; N, 7.79.

Tosylate **10b** was isolated as colorless crystals, mp 90–92 °C.

9,9-Dichloro-*exo*-pentacyclo[5.4.0.0^{2,6}.0^{3,11}.0^{8,10}]undecan-4-yl Acetate (12). A solution of **3a** (0.50 g) and acetic anhydride (0.65 mL) in 6 mL of pyridine was stirred at room temperature in a stoppered flask for 24 h, poured onto ice, and extracted with pentane (3 × 25 mL). The combined organic layers were washed with cold dilute hydrochloric acid, saturated sodium bicarbonate solution, and brine prior to drying. Removal of solvent left 0.6 g of **11** whose key ^{1}H NMR signals were seen [δ 6.25 (m, 2), 4.96 (dd, J = 7 and 2 Hz, 1), and 1.96 (s, 3)] in $CDCl_3$ solution.

To a solution of **11** (0.6 g) in chloroform was added 50 mg of benzyltriethylammonium bromide and 1.5 mL of 50% sodium hydroxide and the mixture was stirred at room temperature for 60 h. Dilution with water was followed by extraction with chloroform (3 × 15 mL). The combined organic layers were washed with brine, dried, and evaporated to give 750 mg (81.5% overall) of **12**: mp 98–99 °C (from cyclohexane); NMR δ_{Me_4Si} ($CDCl_3$) 5.50 (dd, 1), 3.45–2.5 (br m, 6), 2.4–2.02 (m, 2), 1.92 (s, 3), and 1.84–1.4 (m, 2).

This material was used directly without purification.

9,9-Dichloro-*exo*-pentacyclo[5.4.0.0^{2,6}.0^{3,11}.0^{8,10}] undecan-4-ol (13). To a stirred suspension of lithium aluminum hydride (120 mg) in 10 mL of anhydrous ether was added dropwise a solution of **12** (700 mg) in 10 mL of the same solvent. Stirring was maintained at room temperature for 1 h before sequential introduction of water (0.12 mL), 15% sodium hydroxide solution (0.12 mL), and water (0.36 mL). The precipitated solids were filtered and rinsed well with ether. The combined filtrates were washed twice with brine, dried, and evaporated. There was isolated 560 mg (94%) of **13**; NMR δ_{Me_4Si} ($CDCl_3$) 4.65 (dd, 1), 3.12–2.4 (br m, 6), 2.16–1.95 (m, 2), 1.85 (br s, 1), and 1.78–1.35 (m, 4).

This material was likewise utilized without further purification.

Reductive Dehalogenation of 13. To a solution of sodium metal (0.45 g) in 40 mL of liquid ammonia cooled to −75 °C under nitrogen was added 0.60 g of **13** dissolved in 5 mL of ether. Stirring was maintained for 30 min at this temperature before addition of solid ammonium chloride to discharge the blue color. The ammonia was allowed to evaporate, the residue was partitioned between water and ether, and the aqueous phase was twice reextracted with ether. The combined organic layers were dried and evaporated to afford 0.30 g (74%) of alcohol **10a**, which proved identical with the material prepared earlier.

***endo*-Pentacyclo [5.4.0.0^{2,6}.0^{3,11}.0^{8,10}] undecan-4-ol (15a).** Alcohol **10a** (322 mg) was oxidized with chromium trioxide–pyridine in the predescribed manner to give 78 mg of ketone **14**; IR ν_{max} (neat) 1730 cm^{-1}. Its direct reduction with sodium borohydride (100 mg) was carried out in 3 mL of absolute methanol at 0 °C for 10 min. After stirring at room temperature for 1 h, the mixture was processed in the customary fashion to give 57 mg of oil which crystallized on standing. Preparative gas chromatography on a 6 ft 5% SE-30 column at 110 °C gave 31 mg (39%) of **15a** as colorless crystals; IR ν_{max} (neat) 3340, 1447, 1347, 1330, 1312, 1298, 1110, 1062, 1035, 1010, 910, 827, and 804 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 4.40 (m, 1), 2.90 (m, 6), 2.52 (m, 2), 2.20 (m, 1), 1.81 (m, 1), 1.29 (m, 1), 0.42 (dt, 1), and −0.18 (dt, 1).

The dinitrobenzoate was prepared in the usual manner and obtained in 93% yield as off-white blades, mp 184.5–185.5 °C (from ether).

Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.46; H, 4.50; N, 7.85.

Tosylate **15b** did not crystallize and was utilized in the form of a colorless viscous oil.

Kinetic Measurements for *endo*-Tosylates. In the case of **5b, 8b,** and **15b,** the usual ampule technique was used. Approximately 40 mg of tosylate was dissolved in 10 mL of buffered acetic acid (0.03 M in NaOAc) and transferred in 1.25-mL portions into eight ampules. These were sealed and placed simultaneously into a constant temperature bath. After 15 min, the first ampule was removed and inserted immediately into an ice bath. After 2 min, the ampule was transferred to a room temperature water bath where it was maintained for 3 min. Exactly 1.0 mL of this solution was titrated with 0.0075 M perchloric acid in acetic acid to give V_0; V_∞ was taken after 10 half-lives. Additional ampules were removed at appropriate time intervals and handled comparably. The rate constants were obtained by least-squares analysis of $\ln (V_\infty - V_0/V_\infty - V)$ vs. time with the aid of a Wang computer program.

Kinetic Measurements for exo-Tosylates. The method described by Wiberg[8] was utilized to obtain the solvolysis rates of **6b** and **10b.** The tosylate (~200 mg) was dissolved in 1 mL of dry carbon tetrachloride. Independently, increasing amounts of accurately weighed anhydrous sodium acetate were placed into ten test tubes. The final volume in each was adjusted to 8 mL through addition of anhydrous acetic acid. After 2 drops of a 1% bromophenol blue solution in acetic acid was introduced to each tube, they were stoppered and placed in a constant temperature bath for 15 min. Then a 0.095-mL portion of the tosylate solution was added to the first test tube via syringe and the time for complete indicator change was noted (zero time was taken subsequent to addition). The process was repeated for each test tube, covering a range of 5% reaction. The rate constants were then obtained from a least-squares analysis of $\ln [ROTs]_0/[ROTs]_t$ vs. t.

The following modification was employed for **3b.** Approximately 20 mg of the tosylate was weighed into a vial and 0.1 mL of carbon tetrachloride was added. The vial was placed in a constant temperature together with a second vial containing 8 mL of acetic acid and 2 drops of 1% bromophenol blue in acetic acid. After 15 min, the acetic acid was rapidly transferred to the tosylate solution. A timer was started, 0.100 mL of a standard NaOAc/HOAc solution (viz., 0.9812 × 10^{-3} mmol of NaOAc) was added and the time necessary for complete decolorization was noted. A second 0.100 mL of the NaOAc solution was added and the procedure was repeated. This cycle was extended to cover 20% of reaction and data analysis was achieved as above.

Acetolysis of 8b. A solution containing 0.40 g of **8b** and 0.10 g of sodium carbonate in 10 mL of glacial acetic acid was heated at 71 °C for 40 h. After cooling, neutralization was effected with saturated sodium bicarbonate solution. The products were extracted into ether (3 × 50 mL) and the combined organic extracts were washed with saturated $NaHCO_3$ solution and brine before drying and evaporation. Analysis of the residue (0.20 g) on a 6 ft × 0.25 in. 10% SE-30 column (150 °C) showed the oil to consist of **16b** (98%) and **6c** (2%). Preparative scale isolation gave the pure components.

For **16b:** NMR δ_{Me_4Si} ($CDCl_3$) 4.82 (br s, 1), 2.8–2.05 (br m, 5), 2.00 (s, 3), and 1.9–1.2 (m, 7); *m/e* calcd 192.1154, found 192.1150.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.95; H, 8.48.

For **6c:** NMR δ_{Me_4Si} ($CDCl_3$) 4.83 (m, 1), 3.0–2.05 (br m, 8), 2.00 (s,

3), and 1.95–1.4 (m, 4). This oil proved identical with that obtained from direct acetylation of **6a**.

Acetolysis of 6b. A solution of **6b** (0.10 g) in 6 mL of glacial acetic acid was kept at 71 °C for 25 min. The solvent was removed at 25 °C and 0.1 mm to leave a dark residue (0.085 g) which was dissolved in warm hexane, filtered to remove *p*-toluenesulfonic acid, and cooled to −20 °C. The precipitated solid was recrystallized twice more from hexane to give 0.04 g of pure **16c:** mp 80–80.5 °C; NMR δ_{Me_4Si} ($CDCl_3$) 7.78 (d, J = 5 Hz, 2), 7.31 (d, J = 5 Hz, 2), 4.59 (t, J = 1.5 Hz, 1), 2.75–2.5 (m, 2), 2.45 (s, 3), 2.38 (br m, 3), and 1.8–1.4 (m, 7); *m/e* calcd 304.1133, found 304.1139.

Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.07; H, 6.62. Found: C, 67.16; H, 6.68.

In a second experiment, a mixture of **6b** (0.10 g), anhydrous sodium carbonate (0.05 g), and glacial acetic acid was maintained at 71 °C for 96 h. After the usual workup, there was isolated 0.06 g of **16b** as the only product.

Sequential Reduction–Oxidation of 16b. A solution of **16b** (0.14 g) in 5 mL of anhydrous ether was added dropwise to a stirred slurry of lithium aluminum hydride (0.055 g) in the same solvent (10 mL). After 2 h at room temperature, there followed the usual workup and isolation of 0.08 g of **16a.** The ^1H NMR spectrum of this alcohol was extensively decoupled prior and subsequent to incremental amounts of $Eu(fod)_3$.

Alcohol **16a** (0.03 g) was added to a solution of chromium trioxide (0.12 g) and pyridine (0.19 mL) in 4 mL of methylene chloride and stirred at room temperature for 30 min. The solution was decanted, the residue was rinsed twice with ether, and the combined organic phases were washed with 5% sodium hydroxide solution (3 × 20 mL), 5% hydrochloric acid (3 × 20 mL), and brine. Drying and evaporation afforded 0.025 g of **17:** IR ν_{max} (Nujol) 1780 and 1765 cm^{-1}.

Acetolysis of 5b. A mixture comprised of **5b** (0.40 g), anhydrous sodium carbonate (0.20 g), and glacial acetic acid (10 mL) was kept at 36 °C for 96 h. After the usual workup, 0.23 g of an oil was obtained, VPC analysis of which indicated it to consist of **18b** (70%) and polymeric material (30%). For **18b:** NMR δ_{Me_4Si} ($CDCl_3$) 6.1–5.8 (m, 2), 5.6–5.45 (m, 2), 4.96 (m, 1), 3.4–2.5 (m, 5), 2.17 (s, 3), and 1.7–1.2 (m, 1).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.70; H, 7.36.

Acetolysis of 3b. A solution comprised of **3b** (0.20 g), anhydrous sodium carbonate (0.06 g), and glacial acetic acid (10 mL) was kept at 25.9 °C for 1.5 h. After neutralization with sodium bicarbonate solution, the products were extracted into ether (3 × 40 mL). The combined organic layers were processed in the usual manner to leave a mixture of **18b** (50%), **19a** (5%), and **19b** (≤5%) (combined ^1H NMR and VPC analysis). The volatile acetates were removed under vacuum [25 °C (0.1 mm)] overnight.

One half of the residue (0.06 g) consisting of **19b** was hydrogenated over 10% palladium on charcoal in hexane during 3 h. Filtration and evaporation of solvent left 0.025 g of crystalline **16c.**

The other half of the residue was dissolved in 5 mL of acetic acid containing 0.03 g of sodium carbonate and heated at 70 °C for 41 h. After the usual workup, 0.035 g of an oil was obtained whose only volatile component was **19a;** NMR δ_{Me_4Si} ($CDCl_3$) 6.11 (dd, 1), 5.76 (dd, 1), 4.83 (br s, 1), 2.95–2.80 (m, 4), 2.7–2.0 (br m, 1), 2.02 (s, 3), and 1.95–1.3 (m, 2).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.68; H, 7.69.

Acetolysis of 10b. Subsequent to heating 0.2 g of **10b,** 0.1 g of sodium carbonate, and 7 mL of acetic acid at 71 °C for 72 h and processing the reaction mixture in the usual manner, there was isolated 0.1 g of **20a:** NMR δ_{Me_4Si} ($CDCl_3$) 4.73 (br s, 1), 2.7–1.95 (m, 8), 2.00 (s, 3), 1.90–0.85 (m, 4), and 0.35 to −0.14 (m, 2); *m/e* calcd 134.1095, found 134.1097.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 74.19; H, 9.34. Found: C, 73.94; H, 9.18.

In a second experiment, a 0.05-g sample of **10b** was dissolved in 5 mL of acetic acid and kept at 71 °C for 30 min. After cooling and evaporation of solvent at 20 °C (0.1 mm), there was obtained 0.035 g of a dark oil which was dissolved in warm hexane and filtered to remove *p*-toluenesulfonic acid. On cooling at −20 °C, there was precipitated 0.03 g of **20b:** mp 76.5–77 °C (from hexane); NMR δ_{Me_4Si} ($CDCl_3$) 8.1 (d, 2), 7.5 (d, 2), 4.50 (s, 1), 2.65–1.5 (m, 6), 2.46 (s, 3), 1.3–0.90 (m, 4), and 0.3 to −0.15 (m, 2); *m/e* calcd 316.1133, found 316.1137.

Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.32; H, 6.37. Found C, 68.04; H, 6.45.

Acetolysis of 15b. A solution of **15b** (0.25 g) and anhydrous sodium carbonate (0.1 g) in acetic acid (8 mL) was heated at 71 °C for 30 h. After the usual workup, 0.15 g of an oil was isolated which contained five components in the ratio of 8:40:27:20:5 (6 ft × 0.25 in. 10% SE-30, 160 °C). The individual components were isolated and the most rapidly eluted acetate was shown to be **10c** by spectral comparison. The major constituent was **20a.** The more slowly eluted trio of acetates were unsaturated compounds, the structures of which remain to be ascertained.

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Registry No.—**3a,** 65071-67-2; **4,** 65071-90-1; **5a,** 65137-13-5; **5b** 3,5-DNP derivative, 65137-14-6; **6a,** 65071-91-2; **6b** 3,5-DNP derivative, 65071-92-3; **6c,** 65071-86-5; **8a,** 65137-15-7; **8b** 3,5-DNP derivative, 65137-16-8; **9,** 65071-71-8; **10a,** 65071-74-1; **10b** 3,5-DNP derivative, 65071-75-2; **11,** 65085-84-9; **12,** 65071-76-3; **13,** 65071-77-4; **14,** 65071-78-5; **15a,** 65137-08-8; **15b** 3,5-DNP derivative, 65137-09-9; **16a,** 65071-79-6; **16b,** 65071-80-9; **16c,** 65071-81-0; **17,** 65071-82-1; **18b,** 65071-83-2; **19a,** 65071-84-3; **19b,** 65071-85-4; **20a,** 65102-59-2; **20b,** 65102-60-5; *p*-toluenesulfonyl chloride, 98-59-9.

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Impact of High-Lying σ Orbitals and Extensive Through-Bond Interaction on Chemical Reactivity. 3. Solvolysis of *syn*- and *anti*-Tricyclo[4.2.0.0^{2,5}]octa-3,5-diene Derivatives[1]

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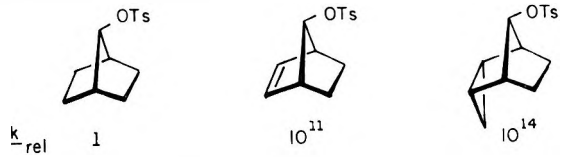
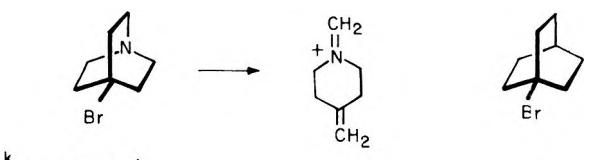
syn- and *anti*-Tricyclo[4.2.0.0^{2,5}]oct-7-en-*exo*-3-ol (**5a** and **9a**) were synthesized by selective hydroboration (9-BBN) of the appropriate cyclobutadiene dimer and converted through diimide reduction to their dihydro derivatives **6a** and **10a**. Kinetic analysis and product determinations for the acetolyses of the respective *p*-toluenesulfonates were carried out. All four compounds ionize some 50 times more slowly than cyclobutyl tosylate and at closely comparable rates. In **5b**, no through-space interaction between the π bond and the developing cationic center is seen to develop, as predictable from photoelectron spectroscopy data which reveal through-bond coupling to dominate. Somewhat unexpectedly, long range electronic transmission through the various σ frameworks, if present, does not demonstrate itself in enhanced solvolytic behavior. The possible product-determining steps are discussed. Finally, comparison of the present data with that available from other cyclobutane-containing sulfonate esters allows conclusions to be made concerning the geometric requirements for effective bicyclobutonium ion intervention.

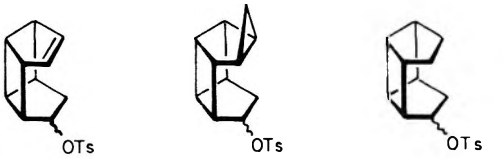
The transmission of electronic effects within molecules can take place "through bonds" or "through space". The level of these interactions is dictated chiefly by structure, geometry, and the types of orbitals involved. The extent and consequences of through-space interaction have received considerable attention and are now reasonably well understood in certain cases, but not others.[2] One classic example is the neutral norbornadiene molecule where the exceptionally favorable interaction of two degenerate π orbitals[3] leads to lowering of the ionization potential relative to norbornene[4] and facilitation of the photocyclization to quadricyclane.[5] A similar through-space orbital mixing can occur in certain carbocations such as the two-electron 7-norbornenyl system[3] where the net stabilization is reflected in an extremely large solvolytic rate enhancement relative to the comparable 7-norbornyl derivative.[6] That the interacting filled orbital need only be rich in p character is evidenced by the solvolytic reactivity of the *endo*-cyclopropyl congener.[7]



In contrast, through-bond coupling is operational in 1,4-diazabicyclo[2.2.2]octane (Dabco).[8,9] Its relationship to 4-bromoquinuclidine has provided a useful basis for analysis of the accelerated solvolytic behavior of the bromide relative to a bicyclo[2.2.2]octyl model and its conversion to products via a σ-bond (Grob) fragmentation.[10]



Unlike norbornadiene, the double bonds in hypostrophene[11,12] do not interact through space, but are instead effectively coupled through high-lying orbitals within the lateral σ bonds.[13] As a consequence, photoclosure to pentaprismane does not operate[11] and electrophilic additions to this diene proceed with extensive skeletal rearrangement.[14] Also, structurally derived *exo*-tosylates undergo acetolysis at significantly enhanced rates.[1]

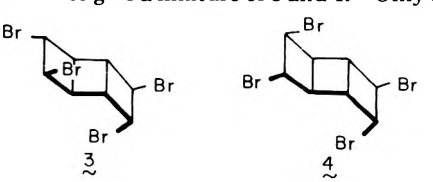


There are also molecules such as Dewar benzene where through-bond and through-space interactions are closely competitive.[15] Thus, extrusion of the CH_2 bridge in norbornadiene results in widening of the dihedral angle on the molecular underside and attenuation of direct π-π interaction such that transmission through the σ framework now gains considerable importance.

Of particular interest at the present time are the *syn*- and *anti*-tricyclo[4.2.0.0^{2,5}]octa-3,7-dienes (**1** and **2**)[16] which

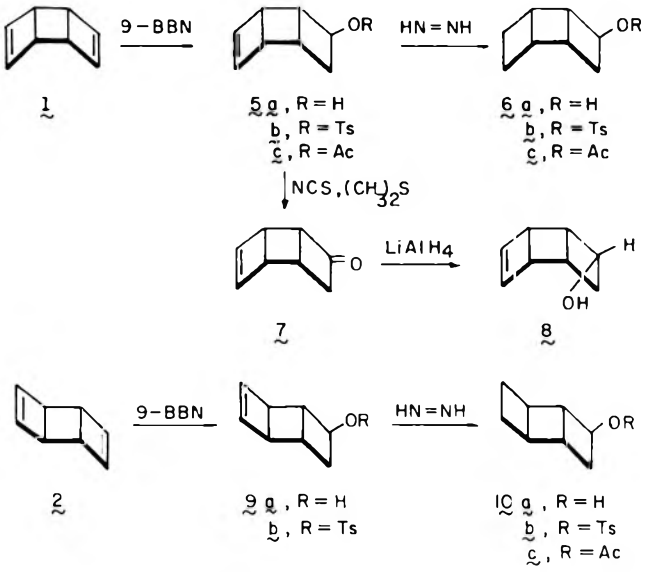
combine fascinating orbital topologies with widely divergent geometries. The electronic structures of these cyclobutadiene dimers have been of substantial theoretical interest and continue to be the subject of controversy.[17-19] Current interpretations of their photoelectron spectral features do not at all agree on precise orbital assignments. The analysis given by Gleiter, Heilbronner, and co-workers assumes a through-space interaction of 0.4 eV for the syn isomer.[17] But this conclusion has been challenged by Bodor et al.[19] Seemingly, conventional photoelectron spectroscopy may not be capable of resolving this dilemma and a different attack on this problem must be awaited.

Development of the chemistry of **1** and **2** has not kept pace with their theoretical scrutiny. The inability to convert a derivative of **1** photochemically to cubane was cited by Criegee in 1962.[20] At a later date, Nenitzescu and co-workers demonstrated that bromination of **2** proceeded *without skeletal rearrangement* to give a mixture of **3** and **4**.[21] Only by heating



0022-3263/78/1943-1299$01.00/0

Scheme I



these tetrabromides with hydrogen bromide in dioxane or acetic acid could isomerization be induced.[21] Finally, when **1** and **2** are thermolyzed, both experience cleavage of the pair of central σ bonds to provide cyclooctatetraene.[22-24]

In the following, we present a detailed investigation into the solvolytic reactivity of four *exo*-tosylates derived from **1**, **2**, and their dihydro derivatives and the course of the ensuing cationic rearrangements. It was anticipated that these derivatives might serve as chemical probes into the nature of those interactions operational in the vicinity of a cationic center and possibly their magnitude.

Results

The stereochemically pure alcohols **5a** and **9a** were prepared by selective hydroboration of **1** and **2** with 9-BBN in tetrahydrofuran[25] (Scheme I). Expectedly,[26] lithium aluminum hydride reduction of the derived *exo*-monoepoxides[23b] did not result in simple C–O bond cleavage. The assignment of exo stereochemistry follows from steric considerations and ^{1}H NMR data. Thus, the >CHOH protons appear as broadened triplets due to coupling to the adjacent methylene hydrogens and minimal interaction with the bridgehead proton ($\theta \approx 90°$). For verification purposes, **5a** was converted to labile ketone **7** by oxidation with *N*-chlorosuccinimide and dimethyl sulfide.[27] Its direct hydride reduction afforded *endo*-alcohol **8** whose α-hydroxyl proton was seen as a broadened multiplet because of added coupling to the bridgehead hydrogen. Additionally, that olefinic proton in **5a** which constitutes the finely spaced triplet at δ 6.50 is now downfield shifted (δ 6.62) as the result of deshielding by the nonbonded electrons on oxygen.

Saturated alcohols **6a** and **9a** could by obtained from their monounsaturated precursors by reduction with excess diimide generated in situ from dipotassium azodicarboxylate.[28] The corresponding tosylates[29] and 3,5-dinitrobenzoates[30] were prepared in classical fashion.

The solvolytic rate constants for these tosylates, as determined in sodium acetate buffered acetic acid, are given in Table I. The values are seen to fall within an exceptionally narrow range. In each case, slightly less than the theoretical amount of acid was liberated. The rate constants were determined using the "infinity titer" observed after 10 half-lives and represent the average of two independent runs. The solvolyses were followed through 1.5–2 half-lives and good first-order plots were obtained in each instance.

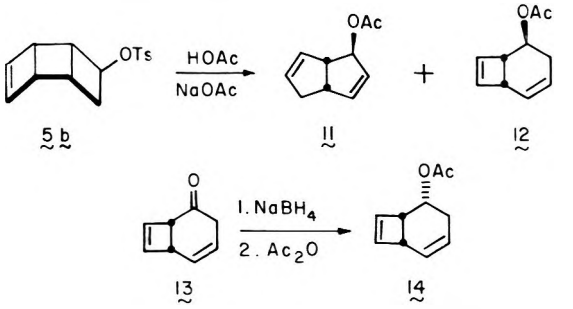
The acetolysis of **5b** proceeded efficiently (95% yield) to give acetates **11** (85%) and **12** (6%) and two unknown compounds (3 and 6%) which could not be adequately separated from **11**

Table I. Rates of Acetolysis in Acetic Acid 0.0510 M in Sodium Acetate

Registry no.	Compd	T, °C	$k(\times 10^5)$, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	k_{rel} (85.2 °C)
65085-72-5	**5b**	68.2	0.91 ± 0.02	27.2	−2	3.6[a]
		79.0	3.75 ± 0.10			
		90.0	10.75 ± 0.27			
65085-73-6	**6b**	79.0	0.95 ± 0.04	26.1	−7	1[a]
		90.0	3.05 ± 0.14			
		100.6	8.97 ± 0.23			
65137-66-8	**9b**	68.2	0.47 ± 0.02	26.2	−6	1.6
		85.2	3.04 ± 0.09			
		100.6	14.82 ± 0.47			
65137-67-9	**10b**	85.2	3.23 ± 0.30			1.7

[a] Interpolated values.

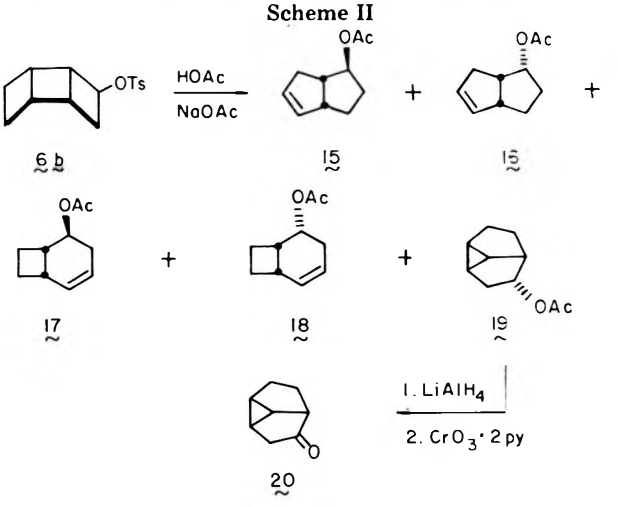
to permit identification. The major component has previously been obtained as the product of acid-catalyzed HOAc addition to semibullvalene and shown to be stable to the solvolysis conditions employed.[31] The ^{1}H NMR spectra of the two samples were identical. The structural assignment to **12** is based solely upon its proton magnetic resonance spectrum and particularly direct comparison with that of **14** formed by sequential sodium borohydride reduction and acetylation of bicyclo[4.2.0]octa-4,7-dien-2-one (**13**).[32] The *endo*-acetate



exhibits a spectrum very similar to that of **12** except for the signal attributable to >CHOAc. The dihedral angle relationships in **14** provides for a high level of spin interaction with proximate hydrogens such that a doublet of triplets (J = 10 and 7 Hz) is clearly visible. In **12**, this signal occurs as a narrow multiplet.

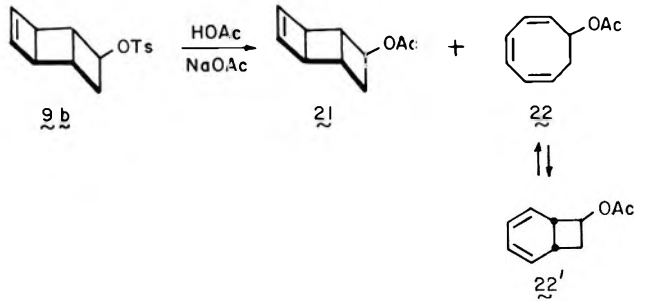
Comparable buffered acetolysis of **6b** gave rise to a five-component mixture consisting of **15** (21%), **16** (11%), **17** (11%), **18** (5%), and **19** (52%) (Scheme II). Subsequent reexposure of each acetate to the reaction conditions resulted in no further structural change. The four less dominant components had been previously prepared in these laboratories[33] and were individually identified by their VPC retention times and ^{1}H

Scheme II



NMR spectra. The spectral features obtained for major product **19** corresponded closely to those reported by Haywood-Farmer and Pincock for the indicated structure.[34] Additional confirmatory evidence of its identity was obtained by reduction to the alcohol followed by oxidation to ketone **20**, which displayed the appropriate carbonyl frequency (1740 cm^{-1}) as well.[34]

Product studies carried out on unsaturated anti isomer **9b** showed it to be converted chiefly to the acetate of retained structure (**21**, 33%) and 7-acetoxy-1,3,5-cyclooctatriene (**22**,



9b 21 22 22'

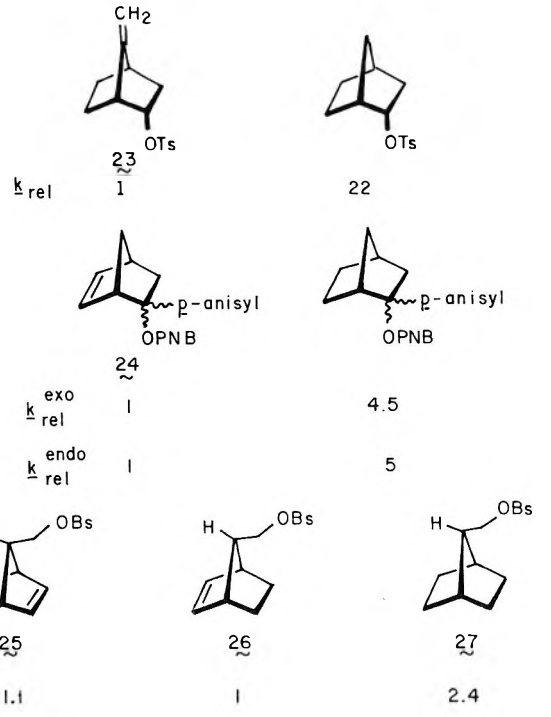
52%). Two more rapidly eluted components were also detected (3 and 12%) but were not characterized due to limited accessibility and serious peak overlap on attempted preparative VPC separation. Both Kröner[35] and Huisgen[36] have previously established that **22** is in equilibrium with bicyclic tautomer **22'** (53% at 60 °C). As with the authentic material, our sample of this acetate likewise exhibited two methyl singlets (~1:1) in the ^1H NMR spectrum. The reduction of cyclooctatrienone with 9-BBN and subsequent acetylation proved to be a serviceable route to **22**, although the yield was quite low (5%). Resubmission of **21** to the original reaction conditions also gave **22**. At the same temperature (90 °C), *syn*-acetate **5c** was converted somewhat more sluggishly to **22** as well. These ring openings may be simple thermal rearrangements, since the temperature involved is sufficiently elevated to promote such transformations. The saturated acetates **6c** and **10c** were inert to such treatment.

The product mixture formed upon acetolysis of **10b** consisted of **17** (66%) and **18** (34%), both of which had been previously identified.

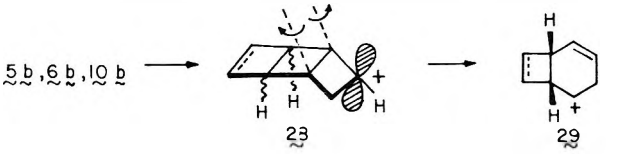
Discussion

It is seen (Table I) that all four tosylates undergo acetolysis at closely comparable rates, the difference between the fastest and slowest at 85 °C being merely a factor of 3.6. One might advance the argument that the similarities in the kinetic behavior of the saturated and unsaturated compounds within a given stereoisomeric subset may arise because of compensatory inductive factors operative principally in the latter. However, such rationalization appears unsatisfactory for several reasons. In unsaturated norbornyl systems such as **23**[37] and **24**,[38] where through-space interaction between the olefinic center and reaction site appears to be unimportant, the adverse inductive contribution of the π system leads to rate retardations on the order of 5–20. The introduction of another intervening carbon atom expectedly ameliorates this effect still more. Thus, Bly found that the acetolysis rates of brosylates **25–27** also fall within a very narrow range, the major product in each case being the acetate of retained structure.[39]

If a destabilizing mechanism of comparable magnitude were operative in the 7-tricyclo[4.2.0.$0^{2,5}$]octenyl ring systems, then the through-bond and/or through-space contributions to enhancement of the rate constants do not exceed a maximum of 2 to 3.5-fold. Clearly, such effects are too small to gain significance.

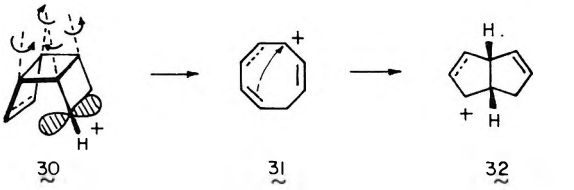


Furthermore, the product studies reveal that no obvious interaction occurs between the proximate π bond in **5b** or the peripheral cyclobutane bonds in **9b** and **10b** with the developing electron-deficient reaction center. Formation of the bicyclo[4.2.0]octyl acetates **12**, **17**, and **18** in three of the examples can be attributed to disrotatory opening of the adjoining internal bond[44] *after ionization* to attain maximum overlap with the vacant p orbital just produced. The resulting homoallylic cation (**29**) is trapped by acetate principally from



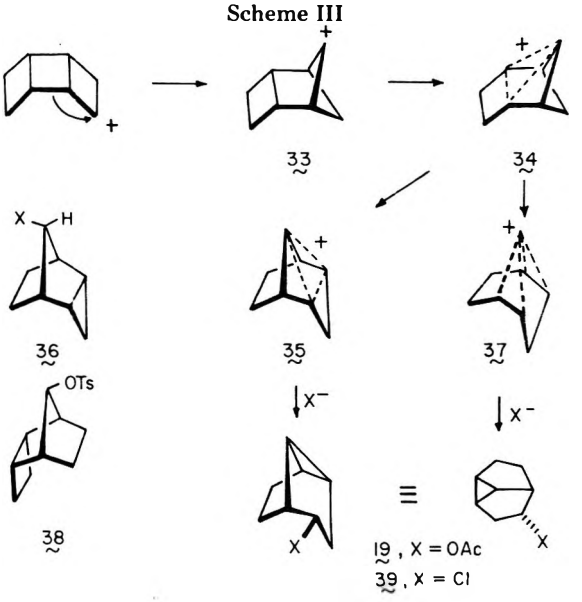
the exo direction as a consequence of prevailing steric conditions, solvent-separated ion pairing, and the like.

The origin of the bicyclo[3.3.0]octane ring system raises an interesting mechanistic question. Since this process occurs only when syn geometry is present, it is tempting to relate this product-forming step to the suitable orientation of the cyclobutane Walsh orbitals in the second distal internal bond such that its rupture occurs concomitantly with the first (cf. **30**). Subsequent transannular cyclization within **31** would give rise to **32**.



The acetolysis of **6b** leads principally to acetate **19**. As with *exo*-bicyclo[2.2.0]hex-2-yl tosylate,[41] ionization appears to be accompanied by lateral carbon–carbon bond migration to give initially **33** (Scheme III). In accord with the established solvolytic behavior of **38**,[45] delocalization of the proximal cyclobutane σ electrons can now be anticipated. Cation **34** is not a likely minimum on this potential surface and can be expected to experience "bridge flipping"[46] to arrive at trishomocyclopropenyl cation **35** or conversion to square-pyramidal ion **37**. The latter species has been generated by ionization of **36**-Cl and **39** and directly observed by NMR

Scheme III



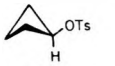
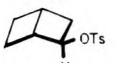
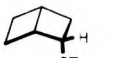
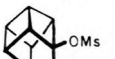
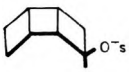
spectroscopy.[47] In any event, ions **35** and **37** are known to trap acetic acid to give **19** as the exclusive product.

The ionization of **9b** leads to appreciable amounts of unrearranged acetate **21**, an observation which could be construed as a reflection of through-bond stabilization. If one were to consider the first-formed secondary carbocation as adequately stabilized by such an electronic mechanism, then capture of solvent with retention of configuration and without structural rearrangement might be expected. But this is not the only interpretation demanded by the experimental findings. Thermal ring opening of **21**, a process shown independently to occur under the reaction conditions, could account for the formation of **22**. While this is certainly a source of the triene, our observation that the ratio of **21** to **22** does not change significantly with time during the initial phases of the acetolysis of **9b** (VPC analysis) suggests that some **22** probably also comes directly from the tosylate.

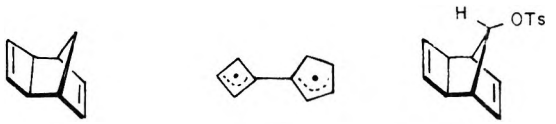
The relatively low solvolytic reactivity of **6b**, **10b**, and *exo*-bicyclo[2.2.0]hex-2-yl tosylate compared to cyclobutyl tosylate (Table II) very likely has its origins in conformational factors. In the simple cyclobutyl example, ionization proceeds from the puckered conformation with anchimeric assistance provided by the β,γ σ bond, the orbital of which attains maximum overlap with the developing empty p orbital and gives rise to a stabilized bicyclobutonium intermediate.[48] In the bi- and tricyclic homologues, conformational flexibility is greatly reduced and disrotatory opening of the central bond concurrent with ionization is prohibited for steric and geometric reasons. However, when the leaving group is endo oriented, these restraints are not in force, bicyclobutonium ions can now intervene, and much of the added steric strain should be reflected in the rate constant. The large rate difference separating the *endo*- and *exo*-bicyclo[2.2.0]hex-2-yl derivatives (Table II) conforms nicely to this interpretation. The somewhat enhanced solvolytic behavior of the secocubyl mesylate has been attributed to steric strain release which develops upon ionization.[48]

The rather unreactive nature of the tosylates examined in the present study would appear to exclude the likelihood that through-bond interactions can be kinetically demonstrated as in the case of hypostrophene derivatives.[1] Neither can the absence of through-space interaction in **5b** be attributed to dissymmetric orientation of the π bond with the developing cationic center. Winstein earlier found that trifluoroacetate **40** is ten times more reactive than the *anti*-7-norbornenyl derivative in spite of such dissymmetry.[49] In addition, the resulting product (**41**) arises from π participation. The mitigating factor in the cation derived from **5b** is more likely the distance between the π bond and the empty p orbital. MINDO calculations for hydrocarbon **1** denote the transannular distance between the two closest nonbonded olefinic carbons to be 2.93 Å.[18] Bly has previously considered 2.8 Å to be beyond the range for possible π anchimeric assistance.[39]

Table II. Relative Solvolysis Rates

Compd	k_{rel}	Ref
	50	40
	5.5	41
	4.4×10^8	42
	13	43
	1	This work
	1.7	This work

The inefficiency of through-bond coupling in a structural framework within which photoelectron spectroscopy suggests facile σ-bond relay of electronic effects has been observed on one previous occasion. Thus, Haselbach[50] and Martin[51] have determined that *anti*-tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (**42**) exhibits through-bond coupling in a manner somewhat comparable to **1**. A chemical consequence of this effect is the ready photolytic cleavage of the C_1–C_2 bond to give the bisallyl



radical **43**.[50] Notwithstanding, the 9-tosyloxy derivative **44** solvolyses eight times more slowly than *syn*-7-norbornenyl tosylate, indicating no accelerating effect due to coupling of the reaction center to the cyclobutenyl double bond via C_1–C_2 and C_5–C_6.[52]

The present results indicate that through-bond effects which are clearly evident upon photoelectron spectral analysis of a hydrocarbon system need not necessarily become apparent during solvolysis of a suitably functionalized derivative. Primary detractants from our more lucid understanding of bond assistance effects are steric factors and strain relief, which operate along a given reaction pathway. Understandably, these can sometimes mask those orbital interaction effects being sought and seriously cloud the mechanistic picture. However, a second, more serious complication is inherent to the present treatment. In all circumstances, neutral molecules have been employed as electronic models for the structurally related cations. But the former do not possess the added vacant p orbital which characterizes the latter. Since this p orbital is truly the focus of our interest, the parent systems do

not qualify as true models. This conclusion implies that each individual cation should be analyzed by computational methods in its own right, without necessary regard for the electronic properties of its hydrocarbon congener. Under these circumstances, a more direct correlation with solvolytic behavior might be seen.

Experimental Section

The ^1H NMR spectra were obtained with Varian T-60, Varian A-60A, and Bruker 90 (FT) spectrometers and apparent splittings are given in all cases. The Bruker 90 spectrometer was also employed for the recording of ^{13}C spectra. Mass spectral measurements were made on an AEI-MS9 spectrometer at an ionizing potential of 70 eV. Preparative VPC work was done on a Varian Aerograph A90-P3 instrument equippped with a thermal conductivity detector. A 6 ft × 1/4 in. column packed with 10% OV-11 on 60/80 mesh Chromosorb G at 115 °C was used unless otherwise stated. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

***syn*-Tricyclo[4.2.0.0^{2,5}]oct-7-en-*exo*-3-ol (5a).** To a magnetically stirred solution of 1 (2.08 g, 20 mmol) in 50 mL of tetrahydrofuran under nitrogen at 0 °C was added dropwise 45 mL of 0.5 *N* 9-borabicyclononane in tetrahydrofuran. Stirring was continued for 2 h, whereupon 15 mL of 15% aqueous sodium hydroxide solution followed by 15 mL of 30% aqueous hydrogen peroxide were added dropwise and the solution was allowed to warm to room temperature. The tetrahydrofuran was evaporated and the aqueous residue was extracted with ether (3 × 50 mL). The combined ether layers were washed with water (75 mL) and brine (75 mL), dried, and concentrated to leave a yellow oil. Chromatography on silica gel (elution with 15% ether–pentane) yielded a solid which was recrystallized from pentane to give 0.67 g (27%) of **5a** as white needles: mp 52–55 °C; NMR $\delta_{Me_4Si}(CDCl_3)$ 6.50 (m, 2), 4.18 (t, J = 6.0 Hz, 1), 3.40 (m, 2), 2.75 (m, 2), 2.39 (br s, 1), and 2.40–2.00 (m, 2); calcd for *m/e* 122.0732, found 122.0733.

Tosylate **5b** was prepared in the usual way, mp 61–62 °C, as was the 3,5-dinitrobenzoate derivative, mp 127.5–128.5 °C.

Anal. Calcd for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.83; N, 8.86. Found: C, 57.10; H, 4.07; N, 8.64.

***anti*-Tricyclo[4.2.0.0^{2,5}]oct-7-en-*exo*-3-ol (9a).** To a magnetically stirred solution of **2** (2.08 g, 20 mmol) in 40 mL of dry tetrahydrofuran at 0 °C under nitrogen was added dropwise 40 mL (20 mmol) of 0.5 N 9-borabicyclononane in tetrahydrofuran over 1 h. Workup in the predescribed manner yielded 500 mg (25%) of **9a** as a clear oil: NMR $\delta_{Me_4Si}(CDCl_3)$ 6.32 (nm, 2), 4.21 (t, J = 6.2 Hz, 1), 3.13 (nm, 2), 2.40 (s, 1), and 2.36 (m, 4); calcd for *m/e* 122.0732, found 122.0733.

Tosylate **9b** was prepared in the usual way, mp 62–63 °C, as was the 3,5-dinitrobenzoate derivative, mp 151.5–153 °C.

Anal. Calcd for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.2; N, 8.86. Found: C, 57.00; H, 3.90; N, 8.88.

***syn*-Tricyclo[4.2.0.0^{2,5}]octan-*exo*-3-ol (6a).** To a magnetically stirred solution of 1.8 g (14.8 mmol) of **5a** in 150 mL of methanol under nitrogen at 0 °C was added 19 g (100 mmol) of dipotassium azodicarboxylate in one portion. To the stirred slurry was added 15 mL of acetic acid via syringe and stirring was continued until the yellow color of the potassium salt was discharged. The methanol was evaporated, the product was taken up in ether (3 × 50 mL), and the combined organic layers were washed with saturated sodium bicarbonate solution (2 × 100 mL), water (100 mL), and brine (100 mL) before drying and evaporation. There was obtained 1.35 g (85%) of **6a** as a clear oil: NMR $\delta_{Me_4Si}(CDCl_3)$ 4.98 (t, J = 6.0 Hz, 1), 2.93 (m, 4), 2.66 (s, 1), and 2.36 (m, 6); calcd for $C_8H_{12}O$, *m/e* 124.0888, found 124.0890.

Tosylate **6b** was prepared in the usual way, mp 44–45 °C, as was the 3,5-dinitrobenzoate derivative, mp 144.0–144.5 °C.

Anal. Calcd for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.43; N, 8.86. Found: C, 56.57; H, 4.50; N, 8.71.

***anti*-Tricyclo[4.2.0.0^{2,5}]octan-*exo*-3-ol (10a).** To a magnetically stirred solution of 1.1 g (9.0 mmol) of **9a** in 100 mL of methanol at 0 °C under nitrogen was added 13.9 g (72 mmol) of dipotassium azidocarboxylate in one portion. Subsequently, 9.7 mL of acetic acid was added slowly over 1 h and stirring was continued until the yellow color was discharged. Through workup as described above, there was isolated 590 mg (53%) of **10a** as a clear oil: NMR $\delta_{Me_4Si}(CDCl_3)$ 4.26 (t, J = 6.0 Hz, 1), 2.88–1.83 (m, 4), 2.65 (m, 6), and 2.01 (s, 1); calcd for *m/e* 124.0888, found 124.0890.

The tosylate (**10b**) was prepared in the usual way and used directly as a clear oil.

***syn*-Tricyclo[4.2.0.0^{2,5}]oct-7-en-*endo*-3-ol (8).** To a magnetically stirred solution containing 218 mg (1.64 mmol) of *N*-chlorosuccinimide in 10 mL of methylene chloride cooled to 0 °C under nitrogen was added 102 mg (1.68 mmol) of dimethyl sulfide via syringe. A white precipitate formed and the mixture was cooled to −23 °C. Alcohol **5a** (100 mg, 0.82 mmol) in 3 mL of methylene chloride was added in one portion and stirring was continued for 2 h, whereupon 84 mg (0.84 mmol) of triethylamine was introduced. The mixture was allowed to warm to room temperature and poured into ether (15 mL) and water (50 mL). The aqueous phase was separated and the organic layer was washed with water (2 × 25 mL), dried, concentrated, and transferred to a 25-mL round-bottom flask. Lithium aluminum hydride (50 mg, 1.3 mmol) was added and the mixture was stirred at room temperature for 1 h. Saturated sodium sulfate solution was added dropwise until the supernatant liquid became clear and the precipitated aluminum salts were filtered and washed amply with ether. The filtrate was dried and concentrated to leave 30 mg (30%) of 8 as a clear oil: NMR $\delta_{Me_4Si}(CDCl_3)$ 6.62 (nm, 1), 6.40 (nm, 1), 4.16 (m, 1), 3.52 (br d, 2), 2.56 (m, 2), and 2.17 (m, 2).

Kinetics Procedure. A ~0.02 M solution of tosylate (accurately weighed) in 0.0510 N sodium acetate in acetic acid was prepared in a 20-mL volumetric flask. Aliquots of this solution were removed and sealed in glass ampules which had been washed sequentially with 10% hydrochloric acid, 10% ammonium hydroxide, and water, and dried at 70 °C overnight. The ampules were simultaneously placed in a constant temperature bath and after 10 min the first ampule was removed and quenched in ice water. At this point an accurate timer was started. The ampule then was allowed to warm to room temperature for ~5 min and exactly 1.985 mL of solution was removed via an automatic pipet and titrated with standard perchloric acid in acetic acid. Three drops of bromphenol blue was used as indicator and the end point was considered to be reached when the yellow solution turned clear. The remaining ampules were removed at appropriately timed intervals and treated as above. Points were taken through 1–2 half-lives and an infinity titer was taken after 10 half-lives.

Preparative Scale Solvolysis of 5b. A magnetically stirred solution of 1.0 g (3.63 mmol) of **5b** and 530 mg (5.0 mmol) of sodium carbonate in 25 mL of acetic acid was heated at 90 °C for 18 h (10 half-lives). The solution was cooled, poured into 100 mL of water, and extracted with ether (3 × 30 mL). The combined ether layers were washed with 50-mL portions of 10% aqueous sodium hydroxide solution (2×), water, and saturated aqueous sodium chloride solution before decolorization with charcoal, filtration through Celite, drying, and evaporation. There remained 560 mg (95%) of a clear oil, analysis of which by VPC showed four components to be present, two of which could be preparatively separated.

The first compound to be eluted was identified as **12** (3.5%): NMR $\delta_{Me_4Si}(CDCl_3)$ 6.34 (nm, 1), 6.14 (nm, 1), 6.03 (d, J = 4.5 Hz, 2), 5.55 (nm, 1), 3.00 (AA'BB', 2), 2.38 (t with fine splitting, J = 8.0 Hz, 1), and 2.06 (s, 3).

The third component was **11** (85%) as shown by comparison of its ^1H NMR features to those published:[31] NMR $\delta_{Me_4Si}(CDCl_3)$ 6.05 (dd, J = 2.0 and 5.5 Hz, 1), 5.80–5.50 (m, 3), 5.40 (m, 1), 3.65 (m, 1), 3.30 (m, 1), and 2.00 (s, 3); calcd for $C_{10}H_{12}O_2$, *m/e* 164.0837, found 164.0839.

Two other components (3 and 6%) could not be separated in a pure state due to coincidental elution with **11**.

Preparative Scale Acetolysis of 6b. A solution of 1.25 g (4.5 mmol) of **6b** and 500 mg (4.7 mmol) of sodium carbonate in 25 mL of acetic acid under argon was heated at 90 °C for 63 h (10 half-lives). The usual workup yielded 500 mg (68%) of a clear oil which exhibited five peaks upon VPC analysis. These were preparatively separated. The first two compounds to elute were collected together and shown to be **15** (21%) and **16** (11%). The third and fourth components were likewise collected together and identified as **17** (11%) and **18** (5%).

The final acetate proved to be **19** (52%): NMR $\delta_{Me_4Si}(CDCl_3)$ 4.97 (d of t, J = 6.46 and 9.00 Hz, 1), 2.67–1.12 (series of m, 10), and 2.00 (s, 3); ^{13}C NMR ($CDCl_3$) 170.36, 79.82, 44.23, 31.29, 27.07, 26.69, 26.17, 23.71, 21.06, and 19.31 ppm.

Preparative-Scale Acetolysis of 9b. A magnetically stirred solution of 600 mg (2.18 mmol) of **9b** and 500 mg (4.73 mmol) of sodium carbonate in 25 mL of acetic acid was stirred at 90 °C under argon for 26 h (10 half-lives). The usual workup yielded 250 mg (69%) of a clear oil containing four components (VPC analysis). The two major compounds could be separated. The first was identified as **21** (23%) by comparison of ^1H NMR and VPC retention times with those of an authentic sample. The second component was shown to be **22** (65%) by comparison of its ^1H NMR data with those of an authentic sample:[36] NMR $\delta_{Me_4Si}(CDCl_3)$ 5.95 (m, 2), 5.80 (m, 3), 5.15 (m, 1), 3.15–3.00 (m, 1), and 2.50 (m, 2); calcd for $C_{10}H_{12}O_2$, *m/e* 164.0837, found 164.0839.

The two remaining components (5 and 7%) eluted almost simul-

taneously and could not be obtained in a state pure enough for identification.

Preparative-Scale Acetolysis of 10b. To a solution of 1.1 g (4.0 mmol) of **10b** in 10 mL of acetic acid under argon was added 424 mg (4.0 mmol) of sodium carbonate and the solution was stirred at 90 °C for 30 h (10 half-lives). The reaction mixture was processed as before to leave 500 mg (58%) of a clear oil which was purified by preparative VPC. There was isolated a mixture of **17** (66%) and **18** (34%).

***endo*-2-Acetoxybicyclo[4.2.0]octa-4,7-diene (14).** To a solution of 200 mg (1.64 mmol) of bicyclo[4.2.0]octa-4,7-dien-2-one (**13**) in 25 mL of methanol at −20 °C under argon was added 248 mg (6.5 mmol) of sodium borohydride in two 124-mg portions at a 10-min interval. The solution was allowed to warm to room temperature, stirred for 5 h, and poured into 150 mL of water. The aqueous solution was extracted with ether (3 × 50 mL) and the combined ether layers were washed with water (2 × 75 mL) and saturated sodium chloride solution (75 mL) before drying and evaporation. The resulting yellow oil was dissolved in 5 mL of pyridine, 1.4 g (13.8 mmol) of acetic anhydride was introduced, and stirring at room temperature was maintained for 24 h. The solution was poured into 50 mL of water and the water layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with 50-mL portions of water, 10% aqueous hydrochloric acid (2×), saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution prior to decolorization with charcoal, filtration through Celite, drying, and concentration. There remained 238 mg (85%) of the acetate as a clear oil: NMR δ_{Me_4Si} ($CDCl_3$) 6.23 (d, J = 3.0 Hz, 1) 5.70 (m, 2), 4.86 (d of t, J = 7.0 and 10.0 Hz, 1), 3.58 (m, 2), 2.82 (m, 2), and 2.07 (s, 3); calcd for $C_{10}H_{12}O_2$, *m/e* 164.0837, found 164.0839

Control Experiments Concerned with the Stability of Acetates 15–18. A 50-mg (0.09 mmol) sample containing 66% of **15** and 34% of **16** was dissolved in 2 mL of acetic acid and heated at 90 °C under nitrogen for 48 h. The solution was poured into 25 mL of water and extracted with ether (3 × 10 mL). The combined ether layers were washed with 15-mL portions of 15% aqueous sodium hydroxide solution (2×), water, and brine. Drying and evaporation left 30 mg (66%) of a mixture of **5** and **16**, the ^1H NMR spectrum of which was identical with that of the starting sample.

The identical treatment of 30 mg (0.18 mmol) of a mixture of **17** and **18** (66:34) yielded after workup 25 mg (83%) of the unchanged starting mixture.

Control Experiments Concerned with the Stability of Acetates 5c and 21. To a solution of 82 mg (0.2 mmol) of **5c** in 2 mL of acetic acid under argon was added 2.2 mg (0.2 mmol) of sodium carbonate. This solution was stirred at 90 °C for 18 h (10 half-lives). The usual workup afforded 80 mg (98%) of a mixture of starting acetate (55%) and **22** (45%) by integration of the olefinic signals in the ^1H NMR.

Identical treatment of **21** (100 mg, 0.55 mmol) yielded 70 mg (70%) of **22.**

Control Experiments Concerned with the Stability of Acetates 6c and 10c. To 100 mg (0.6 mmol) of **6c** in 5 mL of acetic acid was added 63.6 mg (0.6 mmol) of sodium carbonate and this solution was heated for 48 h at 90 °C under argon. Upon workup, 85 mg (85%) of starting acetate was obtained. Identical treatment of **10c** (200 mg, 1.2 mmol) yielded 160 mg (80%) of unchanged acetate.

Reductive Cleavage and Oxidation of 19. A solution of **19** (30 mg) in anhydrous ether (2 mL) cooled to 0 °C was treated with 19 mg of lithium aluminum hydride and stirred at room temperature for 20 h. Saturated sodium sulfate solution was added dropwise, the precipitate was separated by filtration, and washed thoroughly with ether. The combined filtrates were evaporated to leave the alcohol, which was taken up in dichloromethane (2 mL) and added to a mixture of chromium trioxide (100 mg) and pyridine (158 mg) at 0 °C. After 45 min, the reaction mixture was poured into 10% sodium hydroxide solution and the salts were washed with ether. After further ether extraction, the combined organic phases were washed with 10% hydrochloric acid, water, and sodium bicarbonate solution before drying and evaporation. The resulting pale yellow ketone **20** exhibited a carbonyl stretching frequency at 1740 cm^{-1}.[34]

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Registry No.—**1**, 20380-30-7; **2**, 20380-31-8; **5a**, 65085-74-7; **5b** 3,5-DNP derivative, 65085-75-8; **6a**, 65085-76-9; **6b** 3,5-DNP derivative, 65085-77-0; **8**, 65137-68-0; **9a**, 65137-69-1; **9b** 3,5-DNP derivative, 65137-70-4; **10a**, 65137-71-5; **11**, 36257-89-3; **12**, 65085-78-1; **13**, 65085-79-2; **14**, 65165-51-7; **19**, 24221-98-5; **22**, 16326-82-2.

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Substituent Effects on the Preparations and Thermal Decarboxylations of β-Lactones Derived from the Cycloaddition of Dichloroketene with Monosubstituted Benzaldehydes[1]

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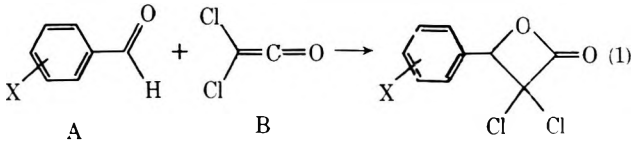
Cycloaddition reactions of dichloroketene and monosubstituted benzaldehydes gave 3,3-dichloro-4-aryloxetan-2-ones in isolated yields of approximately 20–80%. Benzaldehydes substituted with electron-withdrawing groups led to higher yields than benzaldehydes bearing electron-donating substituents. Thermolysis of these β-lactones gave the corresponding β,β-dichlorostyrenes in good yields. Electron-donating groups enhance the rate of decarboxylation. The kinetics of the process were determined for the parent phenyl system and its three monochloro derivatives; the elimination of carbon dioxide is a first-order reaction, probably proceeds in a concerted fashion, and involves a highly polarized transition state.

Part A

There is ample documentation that the reactions of diphenylketene with alkenes to produce cyclobutanone derivatives take place in a concerted fashion.[2] Furthermore, it has been demonstrated that diphenylketene behaves in an electrophilic manner [i.e., that it reacts from its lowest unoccupied molecular orbital (LUMO)].[2b] Similar conclusions have been invoked for cycloadditions involving dichloroketene and olefins.[2c,3] Another cycloaddition process characteristic of ketenes is the formation of 2-oxetanones (β-lactones) from reaction with aldehydes or ketones.[4,5] In connection with other investigations it was necessary to examine what effects, if any, substituents attached to the phenyl ring of benzaldehydes would have on the yields of the β-lactones produced in reactions with dichloroketene. In this report the interesting results of a study on the cycloadditions of dichloroketene with monosubstituted benzaldehydes (eq 1) are discussed.

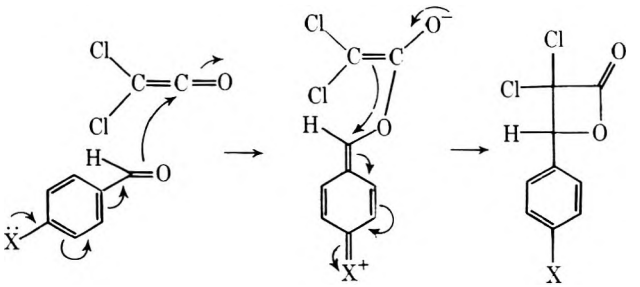


(1)

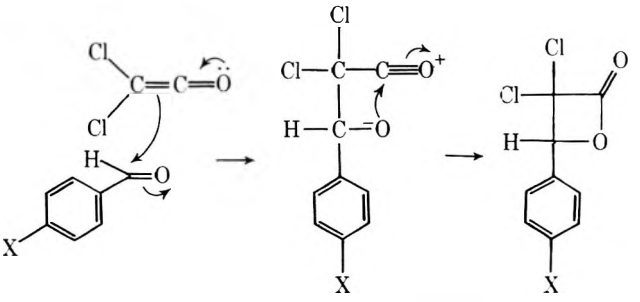
1a-16a

A priori, the substituent on the phenyl ring could influence the cycloaddition process in two ways, as illustrated in Schemes I and II.[6] In the former case (Scheme I), dichloroketene is electrophilic, and electron-donating groups (such as X = OCH_3) would be expected to lead to increased rates of cycloaddition compared to electron-withdrawing substituents (such as X = NO_2). In the latter case (Scheme II), dichloroketene is nucleophilic and electron-withdrawing groups should enhance the reactivity of cycloaddition. Of course, it is also possible that both types of effects could be operative, depending on the nature of the substituent or even that the substituents could have virtually no effect on the cycloaddition process. Interestingly, it has been reported that dichloroketene cycloadds readily to electron-poor aldehydes (such as chloral);[5a,b] yet, it does not react with electron-deficient alkenes (such as acrylonitrile) even though it undergoes cycloaddition very efficiently with electron-rich olefins (such as ethyl vinyl ether).[3a,d]

Scheme I



Scheme II



In Table I are assembled the identities and locations of the substituents attached to the phenyl ring, the important experimental parameters, and the yields of the β-lactones produced. The yields listed in Table I are *isolated yields of crude materials*. Because of the thermal lability of many of the β-lactones, some of the products were contaminated with small amounts of the corresponding β,β-dichlorostyrenes. Similarly, in some cases it was not possible to remove all of the unreacted starting aldehyde by the standard procedure of extraction with aqueous sodium bisulfite solution (probably because of unfavorable electronic effects impeding the formation of the aldehyde/bisulfite addition compound[7]). Fortunately, by integrating the peak areas associated with the NMR signals for the aldehyde formyl proton, the β,β-dichlorostyrene vinyl proton, and the β-lactone ring proton, the relative amounts of these components could be estimated and appropriate adjustments could be made to correct the yields of cycloaddition products. The β-lactones (all of which are oils at room temperature except for the nitrophenyl derivatives **8a–10a**, nitrile **11a**, and acetate **16a**) thus obtained were usually light yellow to golden orange in color (even after treatment with activated carbon). Attempts to purify the liquid cycloadducts by column chromatography using silica gel or by distillation at reduced pressure led to substantial amounts of contamination of the β-lactone by the corresponding β,β-dichlorostyrene as a result of concomitant decarboxylation. Therefore, the β-lactones were characterized by their spectral properties.[8] The infrared spectra showed strong signals at approximately 1860 cm^{-1}, which reflect a 25-cm^{-1} shift to higher frequency (because of the field effects of the adjacent

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Table I. Experimental Conditions and Results for the Preparation of β-Lactones from Monosubstituted Benzaldehydes and Dichloroketene[a]

Entry	Compd	Registry no.	X	Solvent[b]	Temp, °C	B/A[c]	$ZnCl_2$, equiv	Yield,[d] %
1	**1a**	22391-10-2	H	E	3	1	0	32
2	**1a**		H	E	3	1	0.5	30
3	**1a**		H	E	3	1	1	29
4	**1a**		H	E	3	1	1	35
5	**1a**		H	E	−78[e]	1	0	35
6	**1a**		H	E	24	2	0	41
7	**1a**		H	E	24	2	1	45
8	**1a**		H	E	24	2	1	55
9	**2a**	65086-06-8	2′-CH_3	E	3	1	1	19
10	**2a**		2′-CH_3	E	3	1	1	22
11	**2a**		2′-CH_3	E	24	2	0.25	37
12	**2a**		2′-CH_3	M	24	2	0.25	15
13	**3a**	65086-07-9	3′-CH_3	E	3	1	1	24
14	**3a**		3′-CH_3	E	3	1	1	25
15	**3a**		3′-CH_3	E	24	2	0.25	53
16	**3a**		3′-CH_3	P	24	2	0.25	34
17	**4a**	65086-08-0	4′-CH_3	E	3	1	1	26
18	**4a**		4′-CH_3	E	24	2	0.25	44
19	**4a**		4′-CH_3	B	24	2	0.25	33
20	**5a**	65086-09-1	2′-Cl	E	24	1	1	53
21	**5a**		2′-Cl	E	3	1	1	51
22	**6a**	65103-21-1	3′-Cl	E	24	1	1	59
23	**6a**		3′-Cl	E	3	1	1	59
24	**7a**	22391-11-3	4′-Cl	E	24	1	1	52
25	**7a**		4′-Cl	E	24	1	1	59
26	**8a**	65086-00-2	2′-NO_2	E/M	3	1	0	68
27	**8a**		2′-NO_2	E/M	3	1	0	85
28	**8a**		2′-NO_2	E/M	3	1	0.5	73
29	**8a**		2′-NO_2	E/M	3	1	1	73
30	**8a**		2′-NO_2	E/M	3	1	2	46
31	**9a**	65086-01-3	3′-NO_2	E/M	3	1	0	67
32	**9a**		3′-NO_2	E/M	3	1	0.5	65
33	**9a**		3′-NO_2	E/M	3	1	1	64
34	**9a**		3′-NO_2	E/M	3	1	1	71
35	**9a**		3′-NO_2	E/M	3	1	2	52
36	**10a**	65086-02-4	4′-NO_2	E/M	3	1	0.5	65
37	**11a**	65086-03-5	4′-CN	E/M	24	1	0.5	82
38	**12a**	65086-04-6	2′-OCH_3	E	3	1	0	0
39	**12a**		2′-OCH_3	E	3	1	1	0
40	**13a**		3′-OCH_3	E	3	1	0	38
41	**13a**	65086-05-7	3′-OCH_3	E	3	1	0.5	32
42	**14b**[f]		4′-OCH_3	E	24	1	1	23
43	**14b**[f]		4′-OCH_3	E	24	1[g]	1[g]	17
44	**15a**	65085-87-2	3′-$OCOCH_3$	E	3	1	0	36
45	**15a**		3′-$OCOCH_3$	E	3	1	0.5	44
46	**16a**	65085-88-3	4′-$OCOCH_3$	E	3	1	0	29

[a] See eq 1 for reaction. [b] E, ether; M, methylene chloride; P, pentane; B, benzene. [c] Molar ratio of dichloroketene precursor (dichloroacetyl chloride) to monosubstituted benzaldehyde. [d] Isolated yields of crude materials; adjusted to correct for the presence of small amounts of β,β-dichlorostyrenes and unreacted aldehydes; see text. [e] In this experiment the dichloroketene was generated at −78 °C *in the absence of benzaldehyde*, then filtered into a solution of benzaldehyde at −78 °C, and allowed to gradually warm to room temperature. [f] Only the β,β-dichlorostyrene was isolated; see eq 2. [g] In this experiment the dichloroketene was generated by the dechlorination of trichloroacetyl chloride with activated Zn.

dichloromethylene unit[9]) of the characteristic β-lactone carbonyl absorption frequency of about 1835 cm^{-1}.[4b] The ^1H NMR spectra displayed singlet absorption signals for the 2-oxetanone ring hydrogen attached to carbon 4 at 5.68–6.53 ppm, reflecting its benzylic nature and the effects of the adjacent oxy and dichloromethylene groups. The ^{13}C NMR spectra were also in accord with the β-lactone structures. The mass spectra showed relatively small signals for the molecular ions; the base peaks generally occurred at the isotopic cluster *m/e* 110, 112, 114 corresponding to the molecular ion of dichloroketene.[10] In addition to their spectral properties, β-lactones **8a–11a** and **16a** could be purified by recrystallization and, accordingly, were further characterized by consistent elemental analyses. Finally, each of the β-lactones was decarboxylated to provide the corresponding β,β-dichlorostyrenes (see eq 2) which were fully characterized.

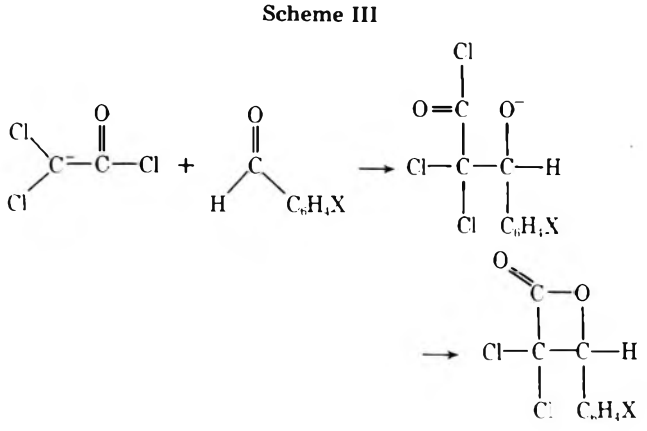
Inspection of the data in Table I clearly reveals that substituent effects are important. For the cycloadditions involving benzaldehyde it is seen that the yields of β-lactone ranged from 29 to 35% and that the presence of freshly fused zinc chloride had virtually no effect on the yield of the product (entries 1–5); the yield was increased somewhat by employing 2 equiv of the dichloroketene precursor (entries 6–8). Introduction of an electron-donating methyl group on the aromatic ring led to slightly reduced yields (19–26%) of the corresponding β-lactones relative to those obtained from benzaldehyde under comparable reaction conditions (entries 9, 10, 13, 14, and 17); again doubling the amount dichloroketene

resulted in higher yields of cycloadduct. Also, in the case of the tolualdehydes, it was found that ether is a better solvent than methylene chloride, pentane, or benzene (compare entires 11, 15, and 18 with 12, 16, and 19, respectively). With the electron-rich *p*-anisaldehyde the yield of the cycloaddition product (only the decarboxylated β,β-dichlorostyrene could be isolated; see Part B) was about 20% (entries 42 and 43). On the other hand, with *m*-anisaldehyde (which according to Hammett σ substituent constants should be slightly electron deficient relative to benzaldehyde[11]) the yield of β-lactone formation was 32–38% (entries 40 and 41). Results analogous to those obtained for the methoxybenzaldehydes were realized with the acetoxybenzaldehydes (entries 44–46). For the moderately electron-withdrawing chlorine substituents (entries 20–25) the yields of the corresponding isomeric β-lactones were significantly higher (51–59%) than those obtained with benzaldehyde. Yields of β-lactone products were further increased (64–85%) by the use of the strongly electron-withdrawing nitro or cyano functionalities (entries 26–37). In these cases it was necessary to utilize a mixed solvent system (ether/methylene chloride) in order to circumvent solubility problems encountered with ether alone. Again, it was observed that the presence of zinc chloride had little effect on the yields of β-lactones (except when 2 equiv were employed).

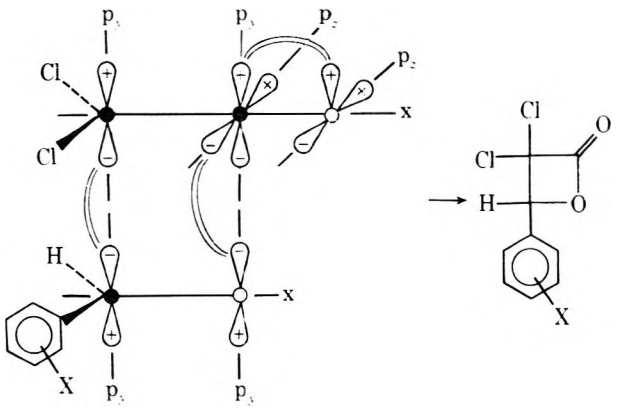
Clearly, the most striking feature of the data collected in Table I is the unmistakable trend that the *more electron withdrawing* the substituent on the benzaldehyde is, the *higher* the yield is for β-lactone formation. The observed reactivity trend is similar to that established for *nucleophilic* additions to carbonyl groups,[12] and suggests that the dichloroketene is behaving in a nucleophilic manner [i.e., the reaction takes place via the highest occupied molecular orbital (HOMO) of the dichloroketene and the lowest unoccupied molecular orbital (LUMO) of the monosubstituted benzaldehyde[13]]. Accordingly, the effects of the aryl substituents on the cycloaddition process are represented better by Scheme II than by Scheme I.[6]

A possible explanation for the interesting results obtained for the cycloaddition reactions tabulated in Table I is that dichloroketene is *not* the reactive species but rather that the chloroacetyldichloro carbanion initiates the cycloaddition process by nucleophilically attacking the aldehyde carbonyl group; subsequent or perhaps simultaneous displacement of the acyl chloride by the aldehyde oxygen would provide the β-lactone structure (Scheme III).[14] In order to test this interpretation, dichloroketene was generated at −78 °C *in the absence of benzaldehyde* by the addition of an ether solution of triethylamine to an ether solution of dichloroacetyl chloride, which resulted in the immediate precipitation of triethylamine hydrochloride; the dichloroketene solution was then filtered into a solution of benzaldehyde at −78 °C and the reaction mixture allowed to warm to room temperature. The 35% yield

Scheme III

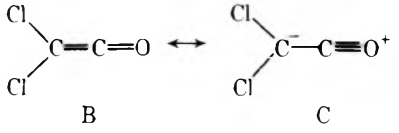


Scheme IV



of β-lactone **1a** from this experiment (Table I, entry 5) was essentially the same as the 32% yield (Table I, entry 1) of **1a** obtained when the reaction was carried out according to the general procedure (see the Experimental Section). Significantly, a nearly quantitative yield of the triethylamine hydrochloride by-product was isolated as the filtration residue. Therefore, it appears that dichloroketene is, in fact, the reactive intermediate in the cycloaddition process.

From the information presently available, it is not possible to ascertain whether the cycloadditions involving monosubstituted benzaldehydes and dichloroketene proceed in concerted or stepwise fashions. There is, of course, compelling evidence which indicates that the reactions between ketenes and double-bond-containing compounds to give four-membered cycloadducts take place in a concerted manner.[2,3,15] Of the two orbital symmetry-allowed processes (the $_{\pi}2_s + _{\pi}2_a$ process[15] and the $_{\pi}2_s + _{\pi}2_s + _{\pi}2_s$ process[2b]) currently relied upon to rationalize the results of ketene cycloadditions, the six-electron $_{\pi}2_s + _{\pi}2_s + _{\pi}2_s$ mechanism is particularly well suited to rationalize the remarkably sensitive substituent effects discovered in the present investigation. In this pictorial representation of the transition state (Scheme IV), an orbital containing a pair of nonbonding electrons from the ketene carbonyl oxygen overlaps with the p_y orbital of the central carbon of the ketene and imparts enhanced electron density to the terminal (chlorine-bearing) carbon of the ketene (thus providing the resonance hybrid C); overlap of the electron-rich



B C

p_y orbital of the terminal carbon of the ketene with the p_y orbital of the carbonyl carbon of the substituted benzaldehyde, followed immediately (or simultaneously if the process is absolutely concerted) by overlap of the p_y orbital of the carbonyl oxygen of the aldehyde with the p_z orbital of the central carbon of the ketene, leads to the β-lactone cycloadduct. The alternative $_{\pi}2_s + _{\pi}2_a$ concerted mechanism[15] cannot be ruled out; however, it would not appear to be able to account for the observed substituent effects in as satisfying a manner as the $_{\pi}2_s + _{\pi}2_s + _{\pi}2_s$ mechanism does.

Part B

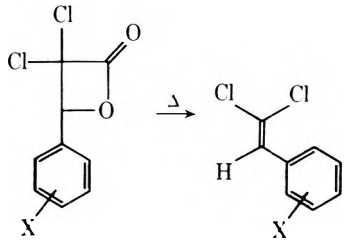
The thermally induced decarboxylation of a β-lactone is a very convenient and efficient synthetic method for the stereospecific introduction of a double bond in an organic molecule.[16] Previous studies have shown for 2-oxetanone itself that the thermal decomposition in the gas phase is a first-order reaction and produces *only* ethylene and carbon dioxide; in addition, the presence of nitric oxide has no effect on the reaction, implicating a nonradical pathway from reactant to

Table II. Experimental Conditions and Results for the Preparation of β,β-Dichlorostyrenes by the Decarboxylation of β-Lactones[a]

Compd	Registry no.	X	Temp, °C	Yield,[b] %	Bp, °C (Torr)	Mp, °C
1b	698-88-4	H	117	71	53–54 (0.25)[c]	
2b	65085-89-4	2′-CH_3	110	73	103–105 (2)	
3b	65085-90-7	3′-CH_3	95	78	117–125 (2)	
4b	4714-37-8	4′-CH_3	110	70	110–127 (2)[d]	35–37[e]
5b	56772-79-3	2′-Cl	165	69	63–64 (0.29)	
6b	65085-92-9	3′-Cl	168	66	69–70 (0.32)	
7b	5263-17-2	4′-Cl	165	78	71–72 (0.38)[f]	
8b	51991-50-5	2′-NO_2	120[g]	21		45–46
9b	65085-93-0	3′-NO_2	175[h]	73		53–55
10b	5281-22-1	4′-NO_2	175[h]	70		90–92[i]
11b	65085-94-1	4′-CN	175[h]	86		75–76
13b	65085-95-2	3′-OCH_3	87	74	156–158 (3)	
14b	41448-64-0	4′-OCH_3	24[j]	23	85–86 (0.50)[k]	27–29
15b	65085-97-4	3′-$OCOCH_3$	87	57		
16b	65085-91-8	4′-$OCOCH_3$	95	63		33–35

[a] See eq 2 for reaction. [b] Isolated yield (not optimized) of purified material. [c] Lit. ("Dictionary of Organic Compounds", 4th ed, Vol. 2, Oxford University Press, New York, N.Y., 1965, p 1000) 103–104 °C (15 Torr). [d] Lit.[20g] 110 °C (15 Torr). [e] Lit.[20a] 40–41 °C. [f] Lit.[20d] 138 °C (5 Torr). [g] In refluxing tetrachloroethylene. [h] In perchlorobuta-1,3-diene. [i] Lit.[20i] 93–94 °C. [j] Product isolated directly from the cycloaddition reaction (eq 1); see text. [k] Lit.[20l] 100 °C (12 Torr).

products.[17] Furthermore, for substrates wherein the stereochemistry of the reaction could be examined, it was found that the decarboxylations are stereospecific cis eliminations.[18] Finally, a few years ago, it was reported that halogenated 2-oxetanones are less susceptible toward decarboxylation than other 2-oxetanones.[19] In the present investigation it has been found that the nature and position of a substituent on the aromatic ring of a 3,3-dichloro-4-phenyloxetan-2-one exert substantial influence on the rate of decarboxylation (eq 2).



(2)

1a–16a **1b–16b**

As indicated in Part A, for the reaction involving *p*-methoxybenzaldehyde and dichloroketene, *only* the β,β-dichlorostyrene **14b** was isolated, demonstrating that the intermediate β-lactone **14a** is extremely susceptible toward decarboxylation, even at room temperature. On the other hand, it was found that for the *p*-nitrophenyl-substituted β-lactone **10a**, prolonged heating at 175–180 °C was necessary to carry out to completion the decarboxylative conversion to the desired β,β-dichlorostyrene **10b**. Clearly, substituent effects are very important for the reactions of eq 2. The other aryl-substituted β-lactones available in this study responded to thermal activation with decarboxylation performances within the limits mentioned above for **10a** and **14a** (Table II). In all cases (except for the o-nitrophenyl β-lactone **8a**) the decarboxylations proceeded smoothly and provided the β,β-dichlorostyrenes in good yields. The β,β-dichlorostyrenes were easily purified by distillation and/or chromatography, and their structures were established by a combination of spectral properties.[8,20]

Qualitatively, the following relative orders of susceptibility toward decarboxylation for the various families of isomeric substituents were found: *p*-$OCH_3 \gg m$-OCH_3; *p*-$CH_3 > m$-CH_3, o-CH_3; *p*-Cl > *m*-Cl, o-Cl; *p*-$NO_2 < m$-$NO_2 <$ o-NO_2. Furthermore, it was qualitatively observed that *p*-$OCH_3 \gg$ *p*-$CH_3 >$ *p*-H > *p*-Cl $\gg$ *p*-NO_2.

In order to gain some quantitative insight on the nature of the substituent effects, the kinetics of the decarboxylation of the parent phenyl-substituted β-lactone **1a** and its three monochlorophenyl derivatives, **5a–7a**, were examined in detail. The rates of decarboxylation of these materials are of such magnitudes that they can be determined conveniently with NMR spectroscopy by measuring the disappearance of the singlet associated with the proton attached to carbon 4 of the β-lactone ring and the appearance of the singlet for the vinyl proton of the β,β-dichlorostyrene product. Fortunately, for **1a,b** and **5a,b–7a.b** the critical ^1H NMR signals were each easily recognizable and well separated from one another as well as from the signals for the aromatic protons. By employing this technique it was not necessary to employ an internal standard; furthermore, the small amounts of impurities present in the β-lactone starting materials did not interfere with the kinetic analyses. The experimental procedure utilized for the rate studies was adapted from the literature.[2b] The neat β-lactone, in an NMR tube, was placed in a constant temperature bath, heated for a definite period of time, placed in an ice water bath to quench the decarboxylation reaction, analyzed by recording the NMR spectrum and obtaining multiple integrations of the signals for the critical protons, and then returned to the constant temperature bath for further reaction.

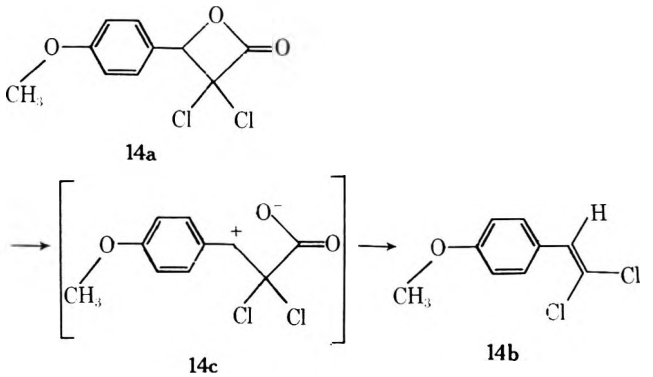
The results of the kinetics experiments are presented in Table III. The first-order rate constants were obtained from least-squares plots of the data. The thermodynamic properties (Table IV) of the decarboxylation reactions were calculated from the Arrhenius equation plots. A plot of the logarithms of the rate constants vs. σ^+ substituent constants[21] gave a least-squares line ($r = 0.998$) with a slope (ρ value) of -3.07.[22] The sign and magnitude of ρ indicate the accumulation of considerable positive character at the benzylic carbon in the transition state of the decarboxylation reaction; the fact that a linear correlation of the rate was obtained with σ^+ constants indicates that substituents can interact via resonance with the reactive site. These considerations are suggestive of a mechanistic interpretation like that shown in Scheme V (illustrated with the *p*-methoxyphenyl system). That the dipolar species **14c** is the transition state for the decarboxylation reaction is indicated by $\Delta S^{\ddagger}$ values (Table IV) which are virtually zero, consistent with a concerted unimolecular elimination process.[23] Furthermore, attempts to intercept the dipolar species **7c** with either electron-rich or electron-deficient olefins (*n*-

Table III. Rate Constants for the Decarboxylation of 3,3-Dichloro-4-phenyloxetan-2-one and Its Three Monochlorophenyl Derivatives at Various Temperatures[a,b]

Compd	X	Temp, °C	$10^5 k$, s^{-1}	r^c
1a	H	76	1.92	0.998
1a	H	82	3.06	0.998
1a	H	85	3.69	0.998
5a	2′-Cl	104	0.294[d]	0.997
5a	2′-Cl	130	2.81	0.997
5a	2′-Cl	144	7.61[e]	0.994
6a	3′-Cl	86	0.222[f]	0.991
6a	3′-Cl	104	1.03	0.997
6a	3′-Cl	130	7.61	1.000
7a	4′-Cl	72	1.29	0.999
7a	4′-Cl	86	2.52	0.997
7a	4′-Cl	88	2.74	1.000
7a	4′-Cl	98	6.00[g]	0.989

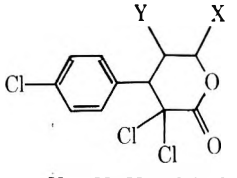
[a] See eq 2 for reaction. [b] The estimated precision for the rate constants is ±4% or better except as noted. [c] Correlation coefficient for least-squares plots of rate data. [d] The estimated precision is ±11%. [e] The estimated precision is ±6%. [f] The estimated precision is ±14%. [g] The estimated precision is ±9%.

Scheme V



14a 14c 14b

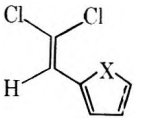
butyl vinyl ether or methyl acrylate, respectively) and produce the substituted valerolactones **17** were unsuccessful; *only* the



17a, X = H; Y = CO_2CH_3
b, X = OC_4H_9; Y = H

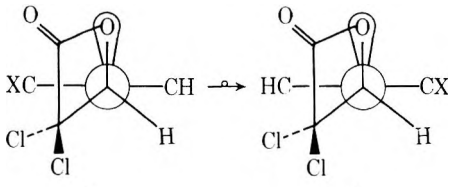
β,β-dichlorostyrene **7b** was produced in each experiment.[24,25]

In line with the facile decarboxylation of the *p*-methoxyphenyl β-lactone **14a** are the results for the cycloaddition reactions of dichloroketene with furfural or thiophene 2-carboxaldehyde. In each case *only* the decarboxylated materials **18b** and **19b** were isolated from the reaction mixtures, reflecting the electron-donating abilities via resonance of the heteroatoms. The low yields (9% for **18b** and 17% for **19b**) are also in accord with the electronic effects discussed previously in Part A.



18b, X = O
19b, X = S

The low relative rate of decarboxylation found for the o-chlorophenyl β-lactone is interesting. In order for the aromatic system to interact via resonance with the electron-deficient benzylic carbon and thus to facilitate the decarboxylation, the conformation of the β-lactone must approach that shown in Newman projection I (or its rotational isomer II). For the



I II

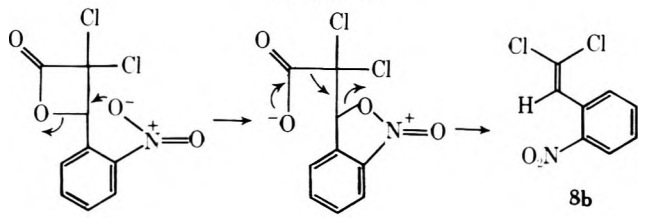
meta- and para-substituted substrates, X in formulas I and II is hydrogen; but for the ortho-substituted derivative, X is the substituent, and accordingly additional steric strain is imparted to the system. Apparently, this enhanced steric hindrance [between the substituent and either the dichloromethylene unit (I) or the β-lactone hydrogen (II)] is sufficiently great so as to drastically diminish any resonance stabilization of the transition state; only the electron-withdrawing inductive effect of the chlorine remains operative, and therefore the rates of decarboxylation of the *o*- and *m*-chlorophenyl-substituted β-lactones are quite similar. In contrast to the isomeric chlorophenyl-substituted β-lactones are the decarboxylations of the isomeric nitrophenyl derivatives. Both the *m*- and *p*-nitro systems **9a** and **10a** were totally unreactive when heated for several hours in refluxing tetrachloroethylene (bp 120 °C); on the other hand, the *o*-nitrophenyl compound **8a** underwent decarboxylation under these conditions. However, the decarboxylation of **8a** was not very clean and only a 21% yield of the β,β-dichlorostyrene **8b** was obtained; this result may be compared to the decarboxylations of **9a** and **10a** which took place smoothly in hexachlorobutadiene at 175–180 °C to give the β,β-dichlorostyrenes **9b** and **10b** in yields of 73 and 70%, respectively. It should also be noted that β-lactone **8a** decomposes to an intractable material merely upon standing (even in a freezer), while **9a** and **10a** are indefinitely stable at room temperature. Perhaps the proximity of the *o*-nitro group to the β-lactone is responsible for both its relatively facile decarboxylation to the β,β-dichlorostyrene

Table IV. Absolute and Relative Rates and Thermodynamic Values for the Decarboxylation of 3,3-Dichloro-4-phenyloxetan-2-one and Its Three Monochlorophenyl Derivatives at 100 °C[a,b]

Compd	X	$10^5 k$, s^{-1}	k_{rel}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/(mol K)	r^c
1a	H	10.4	50	17.4	5.07×10^{-4}	0.999
5a	2′-Cl	0.208	1	24.7	1.91×10^{-1}	0.999
6a	3′-Cl	0.647	3	17.1	3.09×10^{-2}	1.000
7a	4′-Cl	5.92	28	13.9	2.59×10^{-6}	0.982

[a] See eq 2 for reaction. [b] Values for the rate constants were extrapolated from the data presented in Table III. [c] Correlation coefficient for least-squares plots of the Arrhenius equation.

Scheme VI



8a 8b

(Scheme VI) and its spontaneous decomposition to uncharacterized materials.

Experimental Section

Materials. Benzaldehyde, o-, m-, and p-chlorobenzaldehyde, o-, m-, and p-tolualdehyde, and o-, m-, and p-anisaldehyde were commercially available and were distilled before use; o-, m-, and p-nitrobenzaldehyde and p-cyanobenzaldehyde were commercially available and were used without prior treatment; m- and p-acetoxybenzaldehyde were prepared and purified according to literature methods.[26] Dichloroacetyl chloride was commercially available and used as received.

General Comments. Melting points, obtained with a Thomas-Hoover capillary melting point apparatus, and boiling points are uncorrected. ^1H NMR spectra were obtained with a Varian Associates T-60 instrument employing deuteriochloroform solutions with internal tetramethylsilane (Me_4Si) as reference. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer utilizing ^1H decoupling at 80 MHz and simultaneous ^{13}C observation at 20 MHz; in all cases the solvent was deuteriochloroform with internal Me_4Si. Infrared spectra were recorded with a Perkin-Elmer 457 spectrophotometer; liquid samples were measured as neat films, while solid materials were measured as approximately 10% solutions in chloroform. Mass spectra were obtained with a Du Pont CEC 21104 mass spectrometer operated at 70 eV and ambient source temperatures. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. High-pressure liquid chromatography was performed with (1) a Waters Associates ALC-201 HPLC fitted with a 4 ft × 3/8 in. stainless steel column packed with Porasil-A using CH_2Cl_2 as solvent or (2) a Waters Associates Prep 500 system equipped with a PrepPak-500/silica column with 2:1 hexane/methylene chloride as the solvent system. Gas chromatographic analyses and collections were carried out with a Varian Aerograph 1520 instrument equipped with a 5 ft × 0.25 in. aluminum column packed with 20% SE-30 on Chromosorb W.

General Procedure for β-Lactone Preparation. To a 500-mL three-necked round-bottomed flask equipped with an addition funnel charged with 15.0 mL (10.89 g, 0.108 mol) of anhydrous triethylamine diluted to 50 mL with anhydrous diethyl ether, a mechanical stirrer, and a Claisen adapter fitted with a thermometer and an Allihn condenser whose efflux end was connected to a nitrogen bubbler was added 0.100 mol of aldehyde, 100 mL of anhydrous ether, a specified amount of fused $ZnCl_2$,[27] 100 mL of anhydrous diethyl ether, 10.0 mL (15.32 g, 0.104 mol) of dichloroacetyl chloride, and 20 mL of anhydrous diethyl ether. The temperature of the reaction mixture was maintained at 22–24 °C with a room temperature water bath or at 3–5 °C with an ice water bath. With vigorous stirring under a nitrogen atmosphere the triethylamine solution was discharged dropwise over an approximately 1-h period of time. When addition was complete, the mixture was stirred for an additional 1 h, after which time the reaction was processed by vacuum filtration, the residue was washed with diethyl ether, and the combined filtrate and washings were washed with water (1 × 50 mL), dried with anhydrous magnesium sulfate, and concentrated on a rotary evaporator to provide the crude product (contaminated with dichloroketene polymeric materials, unreacted aldehyde, and other minor unidentified impurities) which was treated with a total of 200 mL of pentane to remove polymeric materials. The resulting pentane solution was then washed with H_2O (1 × 50 mL), saturated aqueous sodium bisulfite solution (4 × 50 mL), H_2O (1 × 50 mL), and saturated aqueous sodium bicarbonate solution (2 × 50 mL), dried over anhydrous magnesium sulfate, stirred with activated carbon, and concentrated on a rotary evaporator to provide the desired β-lactone.

For the nitrophenyl and cyanophenyl systems the reaction solvent was 100 mL of methylene chloride and 175 mL of ether in order to circumvent the insolubility of the starting aldehyde in ether alone. In addition, in the processing of the β-lactones **8a–11a, 15a,** and **16a,** ether rather than pentane was used because of solubility considerations.

General Procedure for Decarboxylation of β-Lactones. In a round-bottomed flask equipped with a condenser and a magnetic stirring bar was placed an amount of a β-lactone. The flask was placed in a heated oil bath until NMR/IR spectra revealed that the reaction was complete. The β,β-dichlorostyrene was then isolated and purified by distillation or chromatography.

For the nitrophenyl and cyanophenyl systems the decarboxylations were carried out in chlorocarbon solvents (tetrachloroethylene for **8a** and perchlorobutadiene for **9a–11a**) since attempts to effect the reaction with the pure materials led only to intractable products.

Registry No.—**18b,** 65085-98-5; **19b,** 65085-96-3; benzaldehyde, 100-52-7; o-chlorobenzaldehyde, 89-98-5; m-chlorobenzaldehyde, 587-04-2; p-chlorobenzaldehyde, 104-88-1; o-tolualdehyde, 529-20-4; m-tolualdehyde, 620-23-5; p-tolualdehyde, 104-87-0; o-anisaldehyde, 135-02-4; m-anisaldehyde, 591-31-1; p-anisaldehyde, 123-11-5; o-nitrobenzaldehyde, 552-89-6; m-nitrobenzaldehyde, 99-61-6; p-nitrobenzaldehyde, 555-16-8; p-cyanobenzaldehyde, 105-07-7; m-acetoxybenzaldehyde, 34231-78-2; p-acetoxybenzaldehyde, 878-00-2; dichloroketene, 4591-28-0.

Supplementary Material Available: Spectral and analytical data for the β-lactones **1a–16a** and β,β-dichlorostyrenes **1b–16b** (12 pages). Ordering information is given on any current masthead page.

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Substituent Effects on Reductive Cleavage of *N*-Methylarenesulfonanilides. Cleavage by Sodium Anthracene and Electrochemically at the Vitreous Carbon Electrode

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The relative rates of cleavage of ten para-substituted *N*-methylbenzenesulfonanilides by sodium anthracene in tetrahydrofuran at 25 °C were determined. The rates of those with less electronegative substituents (*p*-dimethylamino through *p*-fluoro) give a moderately good correlation with σ constants, $\rho = 1.91$ ($r = 0.987$). More strongly electron-withdrawing substituents, however, result in a cleavage rate much slower than expected due to reduction of the substituent rather than of the sulfonyl group. Electrochemical reduction in acetonitrile solution at a vitreous carbon electrode proceeds via an irreversible two-electron process. The peak potentials of all the sulfonamides give an excellent correlation with σ^n constants, $\rho = 1.07$ V ($r = 0.995$). Whether this is an eec or ece process is discussed, as well as possible causes for the large differences between homogeneous and electrochemical reduction. A suggested value of σ^n for the *p*-methanesulfinyl group is +0.54.

Arenesulfonamides of secondary amines have been investigated in considerable detail with respect to their reductive cleavage reactions.[2–6] Manousek, Exner, and Zuman showed that 4-cyanobenzenesulfonamide undergoes electrochemical cleavage in aqueous solution at the carbon–sulfur bond (eq 1),[5] while Cottrell and Mann observed only S–N cleavage in

$$ArSO_2NH_2 + 2e + H^+ \rightarrow ArH + {}^-SO_2NH_2 \xrightarrow{H_2O} HSO_3^- + NH_3 \quad (1)$$

electrochemical reduction of several arenesulfonamides in acetonitrile.[4] They proposed an irreversible, two-electron reduction followed by rapid cleavage to two anions (eq 2).

$$ArSO_2NR_2 \xrightarrow{2e} ArSO_2NR_2^{2-} \rightarrow ArSO_2^- + {}^-NR_2 \quad (2)$$

Asirvatham and Hawley noted that Cottrell and Mann's results could also be explained by either the *ece* mechanism shown in eq 3, where the nitrogen- or oxygen-centered radical

$$ArSO_2NR_2 \xrightarrow{e} (ArSO_2NR_2)^{-\cdot} \rightarrow ArSO_2^- + \cdot NR_2 \text{ or } ArSO_2\cdot + {}^-NR_2 \quad (3)$$
$$\downarrow e$$
$$ArSO_2^- + {}^-NR_2$$

would be rapidly reduced at a potential less cathodic than that of the initial reduction, or by a rate-determining disproportionation process (eq 4).[5] Either of these processes would

$$2(ArSO_2NR_2)^{-\cdot} \xrightarrow{slow} ArSO_2NR_2^{2-} + ArSO_2NR_2 \quad (4)$$
$$\downarrow fast$$
$$ArSO_2^- + {}^-NR_2$$

account for the products and *n* values reported.[4] The only arenesulfonamide of a secondary amine (*N,N*-dimethylnitrobenzenesulfonamide) examined by Asirvatham and Hawley, however, underwent reversible, stepwise reduction, yielding the corresponding dianion.[5] Cleavage to amine was not reported.[5]

Kovacs and Ghatak reported that sodium–liquid ammonia reduction of tosylamides leads primarily to C–S cleavage, similar to the results of Manousek et al.,[5] but with a minor pathway involving S–N cleavage.[2] From their data it was not possible to ascertain more information on the mechanism of cleavage. One might expect that reduction of arenesulfonamides with arene anion radicals in ether solvents might proceed in a fashion similar to that in liquid ammonia, but our earlier work using sodium biphenyl, naphthalene, and anthracene in tetrahydrofuran (THF) and dimethoxyethane (DME) showed only the occurrence of S–N cleavage.[3] In addition though we found that the selectivity of cleavage of arenesulfonamides in competition experiments was quite different for sodium anthracene vs. sodium naphthalene.[3] This observation rules out a disproportionation mechanism similar to eq 4 and would be best explained by a mechanism similar to eq 3, where the initial electron transfer is rate determining. Further study of the relative reactivities of different sulfonamides toward sodium anthracene, which would have been useful in refining the cleavage mechanism, was hampered by poor reproducibility.

In this work we wish to present a study of the relative rates of cleavage of a series of *N*-methylarenesulfonanilides by sodium anthracene in THF, a cyclic voltammetric study of the redox behavior of the same series of sulfonamides using the vitreous carbon electrode in acetonitrile, and a discussion of the similarities and differences of these two types of reduction.

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Table I. Relative Rates of Aniline Formation in Sodium Anthracene Cleavage, and Peak Potentials for S–N Reduction of *N*-Methylarenesulfonanilides

Sulfonanilide[a]	Registry no.	Relative rate[b]	*E* vs. SCE (V)[c]
1 (H)	90-10-8	1.0	−2.45
2 (CH_3S)	64999-90-2	1.04	−2.33
3 (CH_3)	599-62-2	0.54	−2.59
4 (F)	360-09-8	0.92	−2.43
5 (Cl)	16358-34-2	1.2[d]	−2.24
6 (Br)	64999-91-3	*d*	−2.26
7 (CH_3O)	16358-36-4	0.19	−2.63
8 [$(CH_3)_2N$]	53973-86-7	0.024	−2.71
9 (CH_3SO)	64999-92-4	0.63	−2.04[e]
10 (CN)	64999-93-5	0.60	−1.76[f]
11 (NO_2)	64999-94-6	0.078	−1.68[g]
12 (CH_3)[g]		0.45[h]	

[a] The para substituent is given in parentheses. [b] Reproducibility was ±5%. [c] Peak potential was measured in the cyclic voltammetric scans on 10^{-3}–5×10^{-3} M solutions of sulfonamide in 10^{-1} M $TBAPF_6$ in acetonitrile at a scan rate of 200 mV/s. [d] Dehalogenation occurred in competition with S–N cleavage. [e] Exhibited irreversible peak at −2.73 V as well. [f] Exhibited reversible peak at −2.37 V in addition. [g] Also exhibited reversible peak at −0.86 V. [h] Relative rate for *N*-ethyl-*p*-toluenesulfonanilide was used as a reference compound.

Results

Cleavage with Sodium Anthracene. Originally we had tried to determine the relative rates of cleavage of different sulfonamides by straightforward competition techniques,[7] which worked well in a similar study of the reductive cleavage of aryl alkanesulfonates.[8] This technique, adding a small amount of anion radical solution to a solution containing an excess of two or more sulfonamides and determining the amount of reaction of each by measuring the yields of the different amines, easily showed the great differences in selectivity between sodium naphthalene, sodium pyrene, and sodium anthracene.[3] Attempts to obtain reproducible relative rate data with sodium anthracene, however, were unsuccessful until it was discovered that the selectivity was very sensitive to sodium ion concentration.[8] It was found that adding a quantity of sodium salt (sodium perchlorate) about equal to the total concentration of sulfonamides (ca. 0.2 M) in the competition mixture allowed quite reproducible results to be obtained. Without this sodium ion buffer not only was reproducibility quite poor, but selectivity between different sulfonamides also appeared to be much lower. The poor reproducibility in the absence of sodium buffer is probably a result of rapidly changing reaction rates as the sodium ion concentration changes from 0 to ca. 0.04 M during the competition experiment.

The cause of this effect is almost certainly related to the state of ion pairing of the anthracene anion radical in THF. Both ESR and conductimetry data have shown that sodium anthracene is largely ion paired in THF,[10,11] and it is to be expected that ion-paired species should be less reactive (and therefore more selective) toward electron-transfer reactions than free ions.[12] An attractive explanation for our results would be that free anthracene anion radical is present at very low sodium anthracene concentrations and cleaves sulfonamides in a much less discriminating fashion than do ion-paired species; buffering with sodium perchlorate merely keeps the equilibrium shifted toward ion-paired species throughout the competition experiment. On the other hand, Bank and Bockrath, through a kinetic analysis of the effect of sodium tetraphenylboron on the rate of reaction of sodium anthracene with water in THF, ruled out the presence of significant amounts of free anthracene ions in concentrations as low as 5×10^{-5} M.[13] Obviously, further work is necessary to define the role of sodium ion in these reactions.

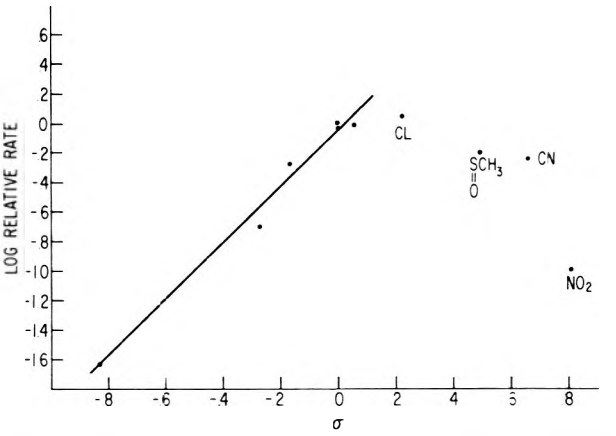
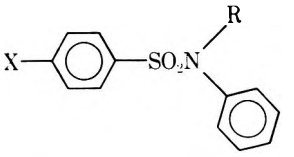


Figure 1. Plot of log of relative rates of sulfonamide cleavage by sodium anthracene vs. σ constants. Least-squares slope for the first portion, 1.91; correlation coefficient, 0.987.

Arenesulfonanilides **1**–**12** were prepared by standard

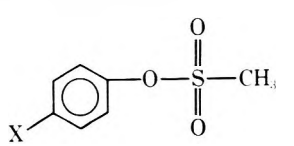


1, X = H; R = CH_3
2, X = SCH_3; R = CH_3
3, X = CH_3; R = CH_3
4, X = F; R = CH_3
5, X = Cl; R = CH_3
6, X = Br; R = CH_3
7, X = OCH_3; R = CH_3
8, X = $N(CH_3)_2$; R = CH_3
9, X = $S(O)CH_3$; R = CH_3
10, X = CN; R = CH_3
11, X = NO_2; R = CH_3
12, X = CH_3; R = CH_2CH_3

techniques, and their relative rates of reaction with sodium anthracene at 25 °C in THF in the presence of 0.04 M sodium perchlorate were determined by competition techniques. The relative rate data for all but **6** are presented in Table I.

From the data in Table I it can be seen that neither strong electron-donating nor electron-withdrawing substituents accelerate the rate of cleavage. Indeed, the two least reactive compounds (toward cleavage) are those with dimethylamino and nitro substituents. For the electron-donating substituents (including fluorine), a Hammett plot may be obtained using σ constants, with a ρ value of +1.91 (r = 0.987). Use of either σ^n or σ^0 gave definitely poorer fits (r = 0.713 and 0.957, respectively). No good correlation of the rates of the sulfonamides with electron-withdrawing substituents could be obtained with any of these substituent parameters (see Figure 1).

The value of ρ is lower than that observed for either of the two steps in S–O cleavage of aryl methanesulfonates (**13**) with sodium anthracene (ca. +6 for the initial electron-transfer step and +3.0 for the product-forming step).[8] The initial electron-transfer step in the cleavage of **13** is closest in nature to



13

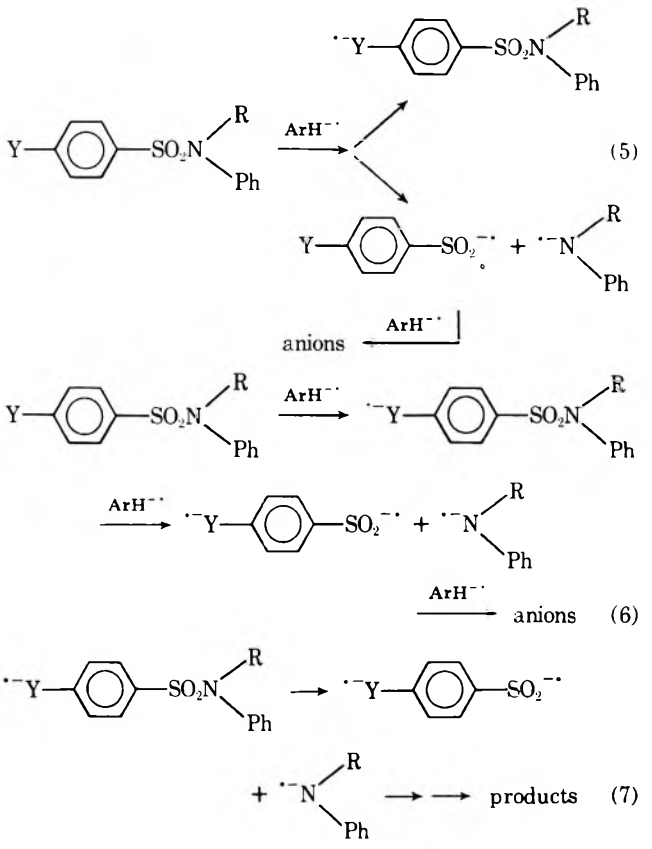
the rate-controlling step in sulfonamide cleavage, and the large difference in reaction constant is striking. In **13** the substituent is also insulated from the sulfonyl group by an additional oxygen atom, which might be expected to attenuate the substituent effect. Probably the best explanation for the large

difference in ρ is that the methanesylfonyl group is inherently less easily reducible than an arenesulfonyl group (alkyl methanesulfonates are not reduced by sodium anthracene but alkyl arenesulfonates are;[14] likewise, anthracene anion radical readily cleaves arenesulfonanilides,[3] but methanesulfonanilides react slowly via a proton-abstraction process[15]), and thus the transition state occurs earlier on the reaction coordinate for the sulfonanilide reaction.

In the case of the *p*-chlorosulfonamide **5** it was shown that dehalogenated, uncleaved sulfonamide **1** was present in the reaction mixture after the competition experiment was performed. This competition between C–Cl and S–N cleavage is similar to that observed between C–X and S–O cleavage in the reaction of halogenated versions of **13** with arene anion radicals[8] and certainly causes the measured reactivity to be less than expected. The bromine-substituted sulfonamide **6** would be expected to be more prone to this side reaction and was not examined. Pertinent to this is the fact that titration plots (yield of amine vs. amount of anion radical added) of **5** and **6** with sodium anthracene in 1,2-dimethoxyethane (DME) solution gave slopes of 0.42 and 0.24, respectively, rather than the value 0.5 expected for 1:2 stoichiometry.[3] This would imply that **5** undergoes some dechlorination prior to S–N cleavage, but that the *p*-chlorobenzenesulfinate ion is fairly stable toward further reaction under these conditions. In the case of **6** the data are probably best interpreted as indicating almost equal reactivity of the C–Br and S–N bonds, with the reactivity of the C–Br bond in *p*-bromobenzenesulfinate ion being considerably less reactive. (The titration plots were measured only to about 30% of the total theoretical yield of amine. At higher extents of reaction one would expect complications due to the buildup of halogenated sulfinate ion and increasing amounts of reaction of this with the electron donor.)

The other sulfonamides with electronegative substituents (**9**, **10**, and **11**) are also almost certainly undergoing reduction of the substituent in competition with the cleavage reaction at the sulfonyl center. The cleavage that is observed may be occurring by either or both of the mechanisms outlined in eq 5 and 6. In eq 5, amine anion is produced in competition with reduction of the substituent in the initial electron transfer; in eq 6, amine anion is generated in a second reduction of the substrate which now bears a negatively charged substituent. This latter sort of electron transfer would be expected to be rather slow since the substituent should now be electron releasing. (It has been reported that the σ^0 constant of a *m*-nitro group changes from +0.70 to about −0.16 upon one-electron polarographic reduction.[16]). A third possibility, use of the electron already in the substituent for a subsequent cleavage reaction at the sulfonyl center (eq 7), might also be considered. In order for this to result in a lesser yield of amine than expected, the cleavage step would either have to have a rate as slow as the time scale of the experiment (a few minutes) or be in competition with other reactions of the reduced substituent.

Some preliminary experiments carried out on sulfonamide **11** with the more potent electron donor sodium naphthalene are pertinent to the question of the cleavage step of **11**. Titration of **11** with sodium naphthalene in DME at 25 °C required ca. 4.7 mmol of anion radical to produce 0.8 mmol of *N*-methylaniline from 1.0 mmol of sulfonamide. Further addition of sodium naphthalene did not increase the yield. A plot of yield of amine vs. amount of anion radical added gives a rather scattered set of points, but some amine is clearly formed after addition of quite small amounts of electron donor. This early production of amine would seem to favor the mechanism given in eq 5. The continued production of amine and the abnormal stoichiometry (the slope of the plot is about 0.2 rather than the expected value of 0.5[3]) would better fit the



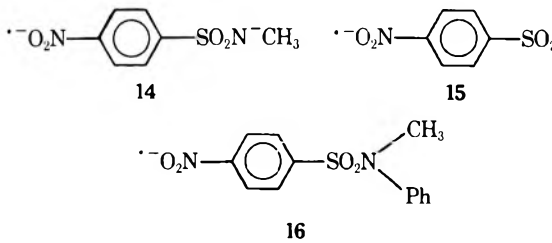
(5)

(6)

(7)

mechanism given in eq 6. (Much anion radical is probably also used up on a variety of other reduction processes typical of aryl nitro groups.[17]) About all that can be concluded is that the pathway of eq 6 almost certainly occurs, but some reaction may be occurring via that of eq 5. The process shown in eq 7 appears very unlikely.

The deep red solution resulting from reaction of **11** with about 2 equiv of sodium naphthalene in DME at 25 °C was examined by ESR and found to give a rather poorly resolved nine-line spectrum. This could be interpreted in terms of hyperfine splittings due to one nitrogen ($a_N \sim 9.6$ G) and a pair of equivalent hydrogens ($a_H \sim 3.2$ G). The poor resolution and broadness of some of the peaks suggest the presence of two or more structurally similar paramagnetic species. Asirvatham and Hawley reported that the hyperfine coupling constants for the ion radicals **14** and **15** were $a_N = 9.41$ G, a_{o-H}



14 **15**

16

$= 3.33$ G, and $a_{m-H} = 1.06$ G, and $a_N = 10.02$ G, $a_{o-H} = 3.33$ G, and $a_{m-H} = 1.07$ G, respectively.[5] It would seem reasonable that our ESR signal might well be the result of a mixture of **15** and **16**.

Cleavage via Electrochemical Reduction. The same series of sulfonamides was examined by cyclic voltammetry, using a vitreous carbon electrode in acetonitrile and tetra-*n*-butylammonium hexafluorophosphate ($TBAPF_6$) as the supporting electrolyte. Several other electrode–solvent systems were examined, but this combination seemed superior, exhibiting an electrochemical window of +1 to −3.0 V vs. SCE.

Most of the sulfonamides showed no electrochemical ac-

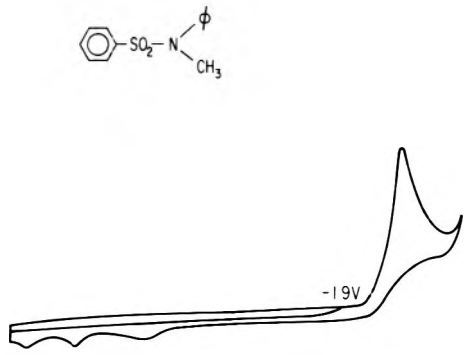


Figure 2. Cyclic voltammogram of *N*-methylbenzenesulfonanalide in acetonitrile with $BTAPF_6$ (0.2 M) as the supporting electrolyte. Scan rate, 200 mV/s; scan direction, negative; initial potential, +1.00 V; final potential, −2.90 V; range, 1 MA.

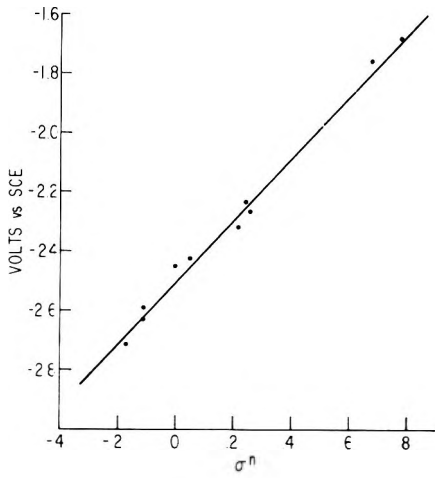


Figure 3. Plot of sulfonamide peak potentials vs. σ^n constants. Least-squares slope, 1.07 V; correlation coefficient, 0.995.

tivity until a single irreversible reduction wave was observed in the vicinity of −2.0 V vs. SCE. On reversal of the scan, oxidation peaks could be observed. Through comparison with known samples, these peaks could be identified as being due to *N*-methylaniline and arenesulfinate ions, the expected cleavage products. A sample scan for **1** is shown in Figure 2. Sulfonamides **5, 6, 9,** and **10** exhibited somewhat different behavior. The scans of **5** and **6** were rather similar to that of **1** except that the areas and shapes of the reduction peaks were inconsistent with a two-electron process as judged by comparison with known two-electron reductions.[18] Reductive dehalogenation was suspected and proved by showing that *p*-bromobenzenesulfinate ion undergoes an irreversible reduction at a potential very close to that of **6**. Therefore, this increase in peak area is probably due to overlapping of the S–N and C–X reduction waves. The methanesulfinyl- and cyano-substituted sulfonamides **9** and **10** also exhibited irregularities. The scan of **9** exhibited two irreversible waves at −2.04 and −2.73 V. Reversal after the first peak showed the usual oxidation waves due to methylaniline and sulfinate salt, so this one can be assigned to reductive cleavage of the sulfonamide group; the peak at the more negative potential is probably due to reduction of the methanesulfinyl moiety. The cyano compound **10** showed an irreversible peak at −1.76 V due to S–N cleavage, followed by a reversible wave at −2.37 V. This is similar to the electrochemical behavior of several *p*-cyanobenzenesulfonamides reported by Cottrell and Mann,[4] and we attribute the second wave to reversible reduction of *p*-cyanobenzenesulfinate ion as did these authors. The cyclic voltammogram of the nitro-substituted compound

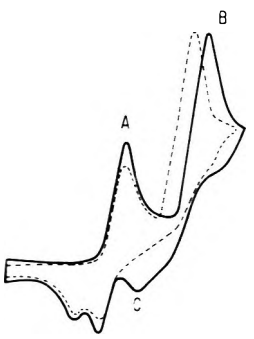


Figure 4. Cyclic voltammogram of *N*-methyl-*p*-nitrobenzenesulfonamide in acetonitrile with $TBAPF_6$ (0.2 M) as the supporting electrolyte; initial potential, 0.0 V; final potential, −2.0 V; scan rate, etc., as in Figure 2. Peak A, reduction of nitro group; peak B, reductive cleavage of S–N bond; and peak C, oxidation of nitrobenzenesulfinate dianion radical. Dashed curve is the cyclic voltammogram in presence of 0.18 M water.

11 also showed unusual features, but this will be discussed later.

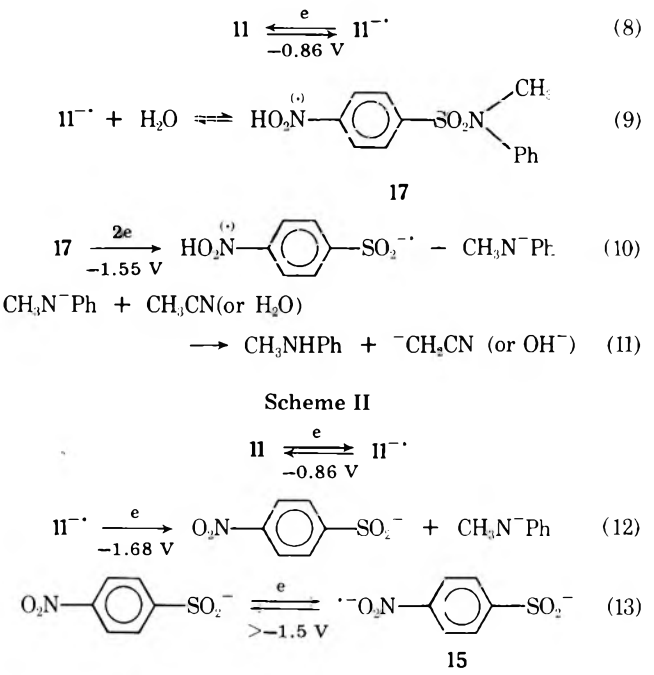
The peak potentials for S–N cleavage of the sulfonanilides are given in Table I. In all cases except for those of **5** and **6** this peak was shown by means of dc pulse polarographic techniques[19] and controlled potential electrolysis to have a current density corresponding to $n = 2$. In Figure 3 the peak potentials are plotted vs. σ^n. This yields a "reaction constant" of "ρ" = 1.07 V, with an excellent correlation coefficient of 0.995. (Although plotted in Figure 3, the value for the nitro compound **11** was not used in determining "ρ", for reasons to be discussed later.) Correlation of peak potentials with σ and σ^0 gave somewhat poorer fits (r = 0.939 and 0.973, respectively). At the time of printing, no literature value for the σ^n constant for the *p*-CH_3SO group could be found. From our data a value of 0.54 can be postulated. This is a reasonable value considering that the methanesulfinyl group is less electronegative than is the methanesulfonyl group,[20] for which a σ^n_p value of 0.686 has been established.[21]

The nitro-substituted compound **11** undergoes a one-electron reversible reduction at −0.86 V vs. SCE, followed by a two-electron irreversible wave at −1.68 V. The magnitude of the oxidation peaks at −1.1 and −0.45 V are dependent on the scan rate and the final potential of the scan. A typical cyclic voltammogram of **11** is shown in Figure 4. Addition of water (0.18 M) to the system alters the scan by causing oxidation peak C to disappear and the position of peak B to shift to a less negative potential. When alumina is added peak C reappears and B reverts to its original position. Peak C has been attributed to oxidation of the anion radical of *p*-nitrobenzenesulfinate ion (**15**).[5] In the presence of water, protonation of the reduced nitro group would seem feasible, and the resulting species (**17**) would not be expected to be oxidized at the same potential. Scheme I is proposed to account for the behavior of **11** in the presence of a proton donor.

If step 9 is fast and equilibrium lies far to the right, the potential necessary for cleavage of the N–S bond should occur at a less negative value. In the absence of a proton donor we postulate the sequence of steps shown in Scheme II. The second irreversible reduction wave was shown to involve the transfer of two electrons. Since reduction of *p*-nitrobenzenesulfinate has been reported to occur at −1.10 V (in DMF), it would probably be reduced as rapidly as formed and give rise to the observed consumption of two electrons (step 13) and the appearance of oxidation peak C on reversal of polarity.

The above argument would indicate an eec (e) process for electrochemical cleavage of **11**, and the question arises as to whether this is general for this class of sulfonanilides. It has

Scheme I



Scheme II

Table II. Properties of Para-Substituted *N*-Methylbenzenesulfonanilides

Substituent	Mp, °C	Lit. mp, °C
H (1)	79–79.5	79[a]
CH_3S (2)	80–81	*b*
CH_3 (3)	92.5–93.5	94[a]
F (4)	65.7–66	67[c]
Cl (5)	95–95.4	*b*
Br (6)	93–94.5	92[d]
CH_3O (7)	109–110.3	109–110[e]
$(CH_3)_2N$ (8)	132–133	132–133[f]
CH_3SO (9)	101.5–102.5	*b*
CN (10)	113–114	*b*
NO_2 (11)	131–132	*b*
CH_3 (12)[g]	84.5–85	87[a]

[a] Z. Rappoport, "Handbook of Tables for Organic Compound Identification", 3rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967, Table XVIII. [b] Satisfactory analytical data (±0.4% for C, H) were reported for these new compounds. [c] R. Nodzu, T. Osaka, H. Kitano, and K. Fukui, *Nippon Kagaku Zasshi*, **76**, 775 (1955); *Chem. Abstr.*, **51**, 17793 (1957). [d] C. S. Marvel and F. E. Smith, *J. Am. Chem. Soc.*, **45**, 2696 (1923). [e] S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson, and P. Wriede, *ibid.*, **89**, 5311 (1967). [f] S. J. Shafer and W. D. Closson, *J. Org. Chem.*, **40**, 889 (1975). [g] *N*-Ethyl derivative.

been argued that a distinction cannot be made between an eec and an ece mechanism for this sort of reaction,[5] but the evidence seems fairly good for our interpretation of the electrochemistry of **11**. Two possibilities seem to exist. One is that the other sulfonamides are reacting by ece processes, and it is fortuitous that the σ^n_p constant of $NO_2^{-\cdot}$ is very close to that of NO_2. This seems rather unlikely. The other is that all are undergoing eec reactions, but in the process of introducing the second electron into $11^{-\cdot}$, the first electron is somehow "moved" from its low energy position in the nitro group into the vicinity of the sulfonamide group, and the full inductive effect of the nitro group comes into play. This sounds even more tortured. If nothing else, our results should serve as a warning toward making general conclusions from electrochemical data obtained from compounds in which nitro groups are present.

Comparison of Homogeneous and Electrochemical Reduction. In general, the data obtained from the sodium anthracene reactions support the originally proposed mechanism, and the correlation of reactivities with Hammett σ constants appears to be typical of these sorts of reactions. Of practical significance, there is no benefit in ease of cleavage derived from introducing substituents more electronegative than hydrogen. Introduction of such substituents merely diverts a portion of the reaction into reduction of the substituent itself, which usually results in making S–N cleavage more difficult. In contrast, the vitreous carbon electrode appears to be much more selective for reduction of the sulfonamide function. In practical terms, even its curious behavior with respect to **11** does not impair its usefulness for regenerating amine from sulfonamide.

An even more striking difference is the correlation of the electrochemical peak potentials with σ^n rather than σ. Particularly noticeable are the data for the *p*-dimethylamino group, which fall extremely close to the correlation line in both Hammett plots; yet, the difference between its σ and σ^n constants is 0.66 units. We thus feel that there is an important difference in reaction mechanism between the two processes. One attractive explanation is that while sodium anthracene reacts with a normal moderately solvated sulfonamide, where the effect of a para substituent will be the usual mix of resonance and inductive interactions, the electrochemical results are probably attributable to heterogeneous surface phenomena at the graphite electrode. If the main site of interaction is the aromatic ring, as might seem reasonable for a vitreous carbon electrode, this may disrupt resonance interactions between substituent and sulfonyl group, while still allowing modest inductive effects.

Experimental Section

Materials and Equipment. Tetrahydrofuran (THF) was reagent grade and was dried by distillation from lithium aluminum hydride and stored under nitrogen. Acetonitrile was spectroscopic grade and was dried either with molecular sieves or alumina before use. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard Model 5750 instrument equipped with flame ionization detectors, using a 6 ft × 0.125 in, 10% silicone rubber (UC-W98) on Chromosorb W column. Triangular wave stationary electrode cyclic voltammetry was performed on a Princeton Applied Research Model 170 electrochemical system using a three-electrode system fitted with a grid to keep the electrodes in the same juxtaposition to maximize the reproducibility of the results. A vitreous carbon or a 2-mm diameter platinum sphere was used as the working electrode. An aqueous saturated calomel electrode was used throughout as the reference. A scan rate of 200 mV/s was employed in obtaining the cyclic voltammograms. The ESR spectra were obtained using a Varian V-4502 PER instrument.

Arene anion radical solutions were prepared and handled as described previously.[3] Their molarity was determined by quenching with water and measuring the amount of dihydroarene produced by GC.[22]

Sulfonamides were prepared by standard techniques from commercially available sulfonyl chlorides and amines, except in the cases noted below. Their properties are described in Table II.

***N*-Methyl-*p*-methanesulfinylbenzenesulfonanilide (9)** was prepared from the corresponding *p*-methylthio compound **2** as follows. To 0.60 g (2.04 mmol) of **2** dissolved in 5 mL of dichloromethane under a nitrogen atmosphere was added 0.49 g (2.16 mmol) of 85% technical grade *m*-chloroperbenzoic acid dissolved in 5 mL of dichloromethane. The mixture was stirred at 22 °C for 40 min, and then 2 mL of 10% aqueous sodium sulfite was added. The mixture was washed with 5% sodium bicarbonate solution until the aqueous extracts remained basic. The organic layer was then dried, the solvent removed under reduced pressure, and the residual solid recrystallized from ethanol, yielding 0.40 g (1.29 mmol, 64%) of white crystals, mp 101.5–102.5 °C.

***N*-Methyl-*p*-cyanobenzenesulfonanilide (12)** was prepared from the corresponding bromo compound **6** after the manner of Friedman and Shechter.[23] A mixture of 8 g of **6** (0.024 mol) and 2.45 g (0.027 mol) of cuprous cyanide was reflexed for 5 h in 20 mL of dimethylformamide. The mixture was then poured into a solution of

Table III. Titration of *N*-Methyl-*p*-chlorobenzenesulfonanilide with Sodium Anthracene in DME at 25 °C

Sodium anthracene, mmol	Yield of N-methylaniline,[a] mmol	Amine/electron-donor ratio
0.308	0.129	0.419
0.532	0.222	0.417
0.720	0.331	0.460
0.910	0.364	0.400
		(0.42 ± 0.01)[b]

[a] Each sample contained 1.23 mmol of sulfonamide in 10 mL of DME. [b] Average value of ratio.

0.6 g of ferric chloride in 17 mL of 1.7 M hydrochloric acid. Extraction with benzene, drying, and concentration yielded a brown material which was purified by liquid chromatography on silica gel (dichloromethane eluent). Recrystallization from ethanol yielded 3.3 g (0.012 mol, 50%) of tan crystals, mp 113–114 °C.

Sodium *p*-bromobenzenesulfinate was prepared from *p*-bromobenzenesulfonyl chloride after the manner of Whitmore and Hamilton.[24] A 62% yield of white crystals, mp 370 °C dec, was obtained by crystallization from water.

Tetra-*n*-butylammonium hexafluorophosphate ($TBAPF_6$) was prepared by a modification of the procedure reported by Ferguson.[25] To a stirred solution of 100 g of tetra-*n*-butylammonium iodide in 700 mL of acetone was slowly added a solution of 50 g of ammonium hexafluorophosphate in 175 mL of acetone. The resulting solution was filtered to remove some of the precipitated ammonium iodide, and then ca. 1 L of water was slowly added to precipitate the $TBAPF_6$. The resulting salt was collected on a filter funnel and washed several times with water. It was then redissolved in 250 mL of acetone along with 5 g of ammonium hexafluorophosphate and reprecipitated by the slow addition of ca. 150 mL of water. The material was collected by filtration and then recrystallized from ethanol–water. The white solid was dried under vacuum (0.5 mm) at 100 °C, affording 75 g (72%) of product, which was used without further treatment.

Competition experiments were carried out by dissolving a total of 0.4 mmol of an *N*-methylsulfonamide and the reference compound 12 in 2 mL of dry THF, which also contained 0.4 mmol of dry sodium perchlorate and ca. 0.02 mmol of *n*-decane, used as an internal standard. The reaction vial was then sealed with a septum and deoxygenated by alternately evacuating and filling with nitrogen. To the stirred solution, at 25 °C, was added slowly ca. 0.44 mL of 0.18 M sodium anthracene solution. After several minutes a few drops of water were added, and the mixture was analyzed by GC. All results are the average of two or more determinations; reproducibility was at least ±5%.

Titrations of sulfonamides with anion radical solutions were carried out in the manner described previously.[3] The data for a typical titration plot are given in Table III.

Electrochemical experiments were carried out as follows. A solution of 0.2 M $TBAPF_6$ in acetonitrile was prepared immediately before use. Using this solution, an amount of sulfonamide was added to give a concentration of 4×10^{-3} M. All measurements were carried out under a nitrogen atmosphere and are the average of three or more determinations. A reference voltammogram of anthracene was run at the start and finish of each series of measurements to ensure against any drift in potential. A scan rate of 200 mV/s was employed.

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Addition of Halogens to Cyclopropylacetylene

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The halogenation of cyclopropylacetylene (1) with chlorine, bromine, trichloramine (NCl_3), and iodobenzene dichloride (IBD) is reported. Chlorine reacts with 1 primarily by an ionic pathway, while bromine can react by either an ionic or radical methanism. IBD and NCl_3 were found to react only by a radical process. The reactivity of 1 with these halogenating reagents is used to make some statements about the relative energy of the transition states in these reactions.

Chlorine (Cl_2),[1a,c] bromine (Br_2),[1b,c] trichloramine (NCl_3),[1d,2] and iodobenzene dichloride ($C_6H_5ICl_2$) (IBD)[1e,2] are known to react with olefins and dienes by an ionic or radical process under the appropriate reaction conditions. The reactions of these halogenating reagents with acetylenes has not been studied extensively. Bromine reacts with acetylenes by an ionic mechanism in acetic acid as solvent.[4] Nazarov and Bergel'son examined the stereochemistry of the radical addition of bromine to a variety of substituted acetylenes.[5] They found that the cis isomers were favored due to the preference of a trans relationship of the bulky substituents in the intermediate 3a.[6] Poutsma reported that chlorine reacts only by

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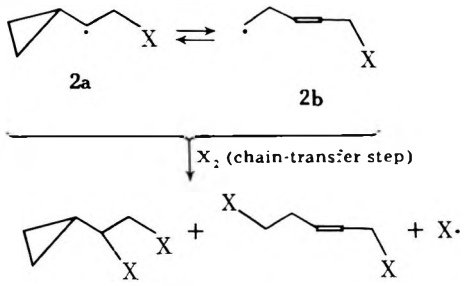
Table I. Halogenation of Cyclopropylacetylene (1)

Entry	Solvent	Mol fraction of 1[a]	Reaction conditions[b]	Halogenating reagent[c]	Percent composition,[d] % 5a or 5b	6a or 6b	7a or 7b	8a or 8b
1	CCl_4	0.02	O_2, dark	Br_2	65	10	4	21
2	CCl_4	0.02	Inhibitor,[e] dark	Br_2	64	12	3	21
3	CH_2Cl_2	0.02	O_2, dark	Br_2	43	19	4	34
4	CCl_4	0.50	N_2, UV	Br_2	44	43	10	3
5	CCl_4	0.05	N_2, UV	Br_2	61	32	7	0
6		Neat	N_2, UV	Cl_2	50	36	6	8
7	CCl_4	0.05	N_2, UV	Cl_2	42	43	3	12
8	CCl_4	0.005	N_2, UV	Cl_2	41	44	5	10
9	c-C_6H_{12}	0.10	N_2, dark	Cl_2[f]	39	48	1	12
10	c-C_6H_{12}	0.02	N_2, dark	Cl_2[f]	35	51	3	11
11	CCl_4	0.02	O_2, dark	Cl_2	37	40	8	15
12	CCl_4	0.05	N_2, UV	IBD	91	2	1	6
13	CCl_4	0.005	N_2, UV	IBD	85	2	3	10
14	CCl_4	0.05	Inhibitor,[e] dark	IBD	[g]	[g]	[g]	[g]
15		Neat	N_2, UV	NCl_3	72	14	5	9
16	CCl_4	0.05	N_2, UV	NCl_3	73	14	4	9
17	CCl_4	0.005	N_2, UV	NCl_3	69	19	8	4
18	CCl_4	0.05	Inhibitor,[e] dark	NCl_3	[g]	[g]	[g]	[g]

[a] Mole fraction of 1 in solvent before the addition of halogenating reagent. [b] The temperature of the reaction mixture was −10 to −5 °C, except for IBD, which was done at 25 °C. The UV light was from a 275-W General Electric sunlamp. [c] Bromine was added neat; chlorine and NCl_3 were added in a CCl_4 or CH_2Cl_2 solutions of known molarity; IBD was added as a solid. [d] Product compositions were determined by VPC analysis on at least two separate runs. [e] The organic inhibitor was 1.0 M 2,6-di-*tert*-butyl-4-methylphenol. [f] Yields of 9.0 and 0.5% of chlorocyclohexane were obtained at 0.10 and 0.02 mol fractions, respectively. Control experiments showed that chlorocyclohexane was not formed by direct chlorination of the solvent. [g] Did not react.

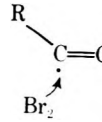
a radical mechanism with 1-butyne to give *trans*-1,2-dichloro-1-butene as the major product[3] (85–90%).

In a recent study of ours[2] on the reaction of various halogenating reagents with vinylcyclopropanes, we reported that 2-cyclopropylpropene reacts with chlorine, bromine, and trichloramine only by an ionic process, whereas IBD reacts primarily by a radical process. Apparently these reagents prefer to react by an ionic process because a very stable cyclopropylcarbinyl cation intermediate can be formed. The

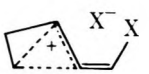


radical process was indicated by an increase in the ring-opened products when the concentration of the radical addend was decreased. This dilution effect was observed because the equilibrium between the classical cyclopropylcarbinyl (**2a**) and homoallyl (**2b**) intermediates was competitive with the chain-transfer step.

Ionic additions to cyclopropylacetylene (**1**) would give a vinylcyclopropylcarbinyl cation intermediate (**4**). This ion should be nonclassical since a nonclassical vinylcyclopropylcarbinyl cation has been reported in solvolysis reactions of 1-cyclopropyl-1-iodoethylene[7a] and similar substrates.[7b] As far as we can determine, the cation intermediate (**4**) has not been formed by the addition of electrophiles to cyclopropylacetylene. Also, we were unable to find a report in the literature of a vinyl radical α to a cyclopropane ring (**3b**).



3a, R = alkyl
b, R = cyclopropyl



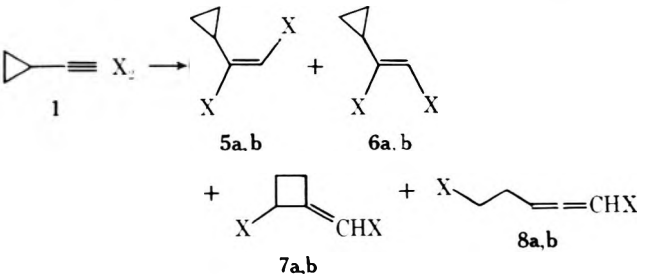
4, X = Br, Cl

In this paper we investigated the halogenation of cyclopropylacetylene (**1**) with Cl_2, Br_2, NCl_3, and IBD.[8] Our purpose was to (1) identify the products obtained from the addition of electrophiles to **1**, and (2) to determine whether these reagents react by an ionic and/or a radical process. We felt that a comparison of these data with that reported earlier for vinylcyclopropanes[2] might allow us to make a statement about the relative energy of the transition states derived from vinylcyclopropanes and cyclopropylacetylene with these reagents.

Results and Discussion

Bromination of **1** under ionic conditions gives 1,2 addition (**5a** and **6a**) and ring-opened products (**7a** and **8a**). The data in Table I show that the 1,2 products are favored by ca. 60–75% (entries 1–3).[9] Addition of bromine to **1** under radical conditions (entries 4 and 5) gives less ring-opened products than bromination under ionic conditions.[10] The increase in *cis*-dibromide **6a** relative to *trans*-dibromide **5a** is typical of radical brominations of acetylenes[5] and is evidence for a radical intermediate in this reaction (compare entries 4 and 5 with 1–3). Molecular chlorine appears to react with **1** predominately by an ionic process since oxygen[11] does not inhibit the reaction or change the product composition significantly (compare entry 11 to 7 and 8).[9,12]

We propose that the chlorinations of **1** with IBD (entries



a, X = Br; b, X = Cl

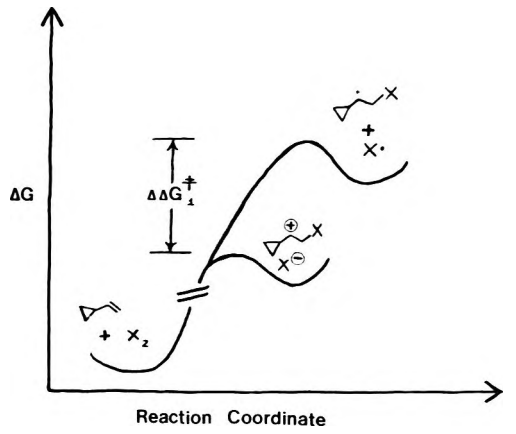


Figure 1. ΔG vs. reaction coordinates for the formation of a cyclopropylcarbinyl radical and cation. $\Delta\Delta G^{\ddagger}_1$ is the energy difference.

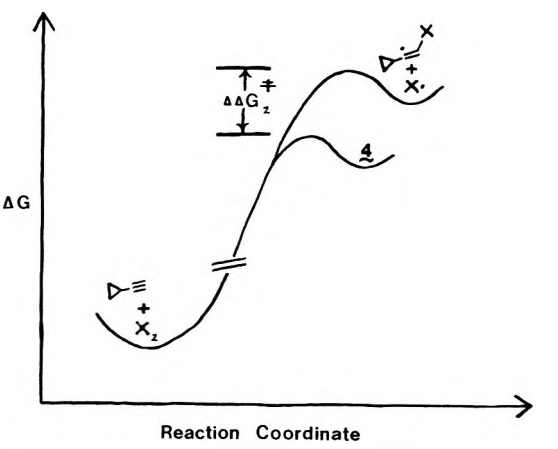
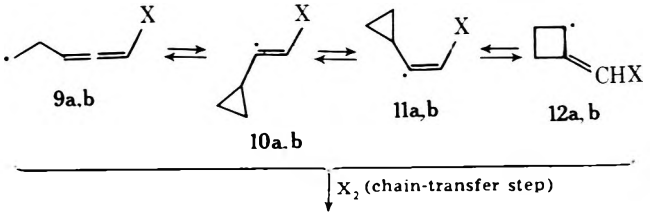


Figure 2. ΔG vs. reaction coordinates for the formation of a vinylcyclopropylcarbinyl radical and cation. $\Delta\Delta G^{\ddagger}_2$ is the energy difference.

12–14) and NCl_3 (entries 15–18) occur by a radical pathway since there is no reaction when an inhibitor is added to the reaction mixture.[13] The smaller amount of *cis*-dichloride **6b** with NCl_3 and IBD compared to *cis*-dibromide **6a** under radical conditions (compare entires 12–18 with 4 and 5) is probably due to a larger steric effect in **10b** than **11b** when these intermediates react in the chain-transfer step.[14]

There is no significant dilution effect when Br_2, NCl_3, or IBD is added to cyclopropylacetylene (**1**) like that observed for the addition of radical halogenating reagents to vinylcyclopropanes.[2] Possibly equilibration of the radical intermediates derived from **1** is faster than the chain-transfer step. Thus, product ratios from these radical reactions are a function of the reactivity of each intermediate (**9a,b–12a,b**) and



5a,b + 6a,b + 7a,b + 8a,b + X·

a, X = Br; b, X = Cl

not the equilibrium concentration as we observed for the intermediates from vinylcyclopropanes.[2]

Trichloramine and iodobenzene dichloride readily react by a radical pathway with **1**, while molecular bromine can react by an ionic or radical mechanism under the appropriate reaction conditions. Our previous work showed that only IBD could be forced to react with a vinylcyclopropane by a radical process.[2] This comparison shows that the energy difference between the formation of a vinylcyclopropylcarbinyl radical and cation ($\Delta\Delta G^{\ddagger}_2$, see Figure 2) is not as large as the energy difference between the formation of a cyclopropylcarbinyl radical and cation ($\Delta\Delta G^{\ddagger}_1$, see Figure 1). Conceivably, $\Delta\Delta G^{\ddagger}_1$ is greater than $\Delta\Delta G^{\ddagger}_2$ due to the unusual stability of a nonclassical cyclopropylcarbinyl cation intermediate.

Experimental Section

General. Cyclopropylacetylene (**1**) was prepared from the dibromide of vinylcyclopropane as reported by Slobodin.[15] Vinylcyclopropane was prepared from the tosylhydrazone of methylcyclopropyl ketone.[16] Trichloroamine[17] and iodobenzene dichloride[18] were prepared as described in the literature. All other reagents and solvents were obtained commercially. Ionic conditions were low mole fractions of olefin, the absence of light, and added inhibitor.[11] Radical conditions were high mole fractions of olefin, the removal of oxygen by nitrogen gas, and ultraviolet light. The light was from a 275-W General Electric lamp. When the reaction was complete, the mixture was concentrated to about 0.3 mL at 25 °C on a rotary evaporator. The crude product mixture was transferred to an NMR tube, and 20–30 μL of a 1.0 M solution of benzene in carbon tetrachloride was added as a standard. Reaction yields were determined by NMR integration. Product ratios were determined by VPC analysis with a Hewlett-Packard 5730 flame ionization chromatograph on a 10 ft × 0.25 in stainless steel column of 5% SE-30 on 80–100 Chromosorb W.[19] Collection of products by VPC was accomplished with a Varian aerograph on a similar column except 12 ft × 0.25 in. NMR spectra were obtained on a Varian T-60A spectrometer.

Reaction of Bromine with 1. To 66 mg (1.0 mmol) of **1** in a weighted amount of solvent so as to obtain the mole fraction listed in Table I at −10 to −5 °C was added 100 mg of neat bromine. The yield by NMR analysis was ca. 50 and 80% under radical and ionic conditions, respectively. Product ratios by VPC are reported in Table I. The products were collected by preparative VPC and had the following retention times on the analytical column: $t_R^{76°C}$ = 16, 21, 24, and 35 min for **5a, 6a, 7a,** and **8a,** respectively. The products had the following NMR spectra: **5a** (CCl_4), δ 0.92 (m, 4 H), 2.05 (m, 1 H), 6.43 (s, 1 H); **6a** (CCl_4), δ 0.75 (m, 4 H), 2.63 (m, 1 H), 6.65 (d, J = 1.0 Hz, 1 H); **7a** (CCl_4), δ 2.37–3.07 (m, 4 H), 4.87 (m, 1 H), 6.08 (m, 1 H); **8a** (CCl_4), δ 2.72 (m with apparent q of d, J = 6.0, 2.5 Hz, 2 H), 3.37 (t, J = 6.0 Hz, 2 H), 5.37 (apparent q, J = 6.0 Hz, 1 H), 5.95 (m, 1 H).

Reaction of Chlorine with 1. To 66 mg (1.0 mmol) of **1** in a weighed amount of solvent (Table I) at −10 to −5 °C was added a 1.8-mL solution of 0.39 M chlorine in carbon tetrachloride. The yields determined by NMR analysis varied from 50 to 80%. Product ratios were determined by VPC on the analytical column with the following retention times: $t_R^{52°C}$ = 8.5, 11.5, 12, and 18 min for **5b, 6b, 7b,** and **8b,** respectively. The products gave the following NMR spectra: **5b** (CCl_4), δ 0.92 (m, 4 H), 2.55 (m, 1 H), 6.18 (s, 1 H); **6b** (CCl_4), δ 0.80 (m, 4 H), 2.2–2.8 (m, 1 H), 6.17 (d, J = 1.0 Hz, 1 H); **7b** (CCl_4), δ 2.1–2.9 (m, 4 H), 4.8 (m, 1 H), 6.20 (m, 1 H); **8b,** δ 2.62 (m with apparent q of d, J = 6.0, 2.5 Hz, 2 H), 3.60 (t, J = 6.0 Hz, 2 H), 5.70 (apparent q, J = 6.0 Hz, 1 H), 6.10 (m, 1 H).

Small amounts of chlorocyclohexane (0.5 and 9.0% at 0.02 and 0.10 mol fractions, respectively) were obtained when the chlorination was carried out in cyclohexane as solvent. Control experiments showed that molecular chlorine does not chlorinate cyclohexane under the conditions of this reaction (under nitrogen and the absence of light).

Reaction of Trichloramine with 1. The reaction was carried out as described above for the chlorination of **1**. Trichloramine[17] was added as a 0.60-M solution in carbon tetrachloride. The reaction mixture was stirred for 10 min at −10 to −5 °C and then concentrated and analyzed as described above. Analysis by NMR showed yields of about 60%. The product ratios are listed in Table I.

Reaction of Iodobenzene Dichloride with 1. To 66 mg (1.0 mmol) of **1** in a weighed amount of carbon tetrachloride (Table I) at 25 °C with stirring was added 190 mg (0.69 mmol) of IBD. The reaction mixture was stirred for 15 min and then concentrated and analyzed as described above. Product ratios are listed in Table I.

Acknowledgment. Support for this work was provided by Research Associates of Point Loma College.

Registry No.—**1**, 6746-94-7; **5a**, 64871-18-7; **5b**, 64871-19-8; **6a**, 64871-20-1; **6b**, 64871-21-2; **7a**, 64871-22-3; **7b**, 64871-23-4; **8a**,

64871-24-5; 8b, 64871-25-6; Br_2, 7726-95-6; Cl_2, 7782-50-5; IBD, 932-72-9; NCl_3, 10025-85-1.

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(8) Our investigation of the halogenation of vinylcyclopropane (ref 2) included a study of methyl hypochlorite. We were unable to isolate any addition products or a propargyl chloride product when cyclopropylacetylene was treated with methyl hypochlorite in a nonpolar solvent.

(9) Cyclobutyl and allenic products are also formed in the solvolysis of 1-cyclopropyl-1-iodoethylene in acetic acid at 25 °C. Cyclopropyl products are also the major components (97%) of the solvolysis reaction (see ref 7a).

(10) Products derived from **11a,b** are interesting since the saturated intermediates (**2a,b**) do not rearrange to the the cyclobutyl intermediate (see ref 2).

(11) Oxygen is known to be a very effective inhibitor of the radical reaction with molecular chlorine (see ref 1a).

(12) There is a minor radical component participating in this reaction since small amounts of chlorocyclohexane were obtained when cyclohexane was used as the solvent under reaction conditions which do not chlorinate cyclohexane (see the Experimental Section)

(13) The observation that 2,6-di-*tert*-butyl-4-methylphenol inhibits the reaction of trichloramine with **1** is curious since Kovacic[1d] was unable to inhibit the radical reaction of trichloramine with alkenes. It appears that the chain-transfer step is slower with alkynes than with alkenes. The discussion above on the dilution study also gives support for a slow chain-transfer step with **1**.

(14) A similar steric effect for IBD and NCl_3 was observed when cyclopentadiene was treated with these radical halogenating reagents: see V. L. Heasley, G. E. Heasley, K. D. Rold, and D. B. McKee, *J. Org. Chem.*, **41**, 1287 (1976).

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(19) Control experiments were performed to show that rearrangement of the products did not occur. Pure compounds were reinjected into the VPC instrument and found to be stable under our analysis conditions. The appearance of the baseline between well-separated peaks of the isomers on our analytical column also ruled out on-column rearrangement. The area/weight response factors for our isomers were similar on the hydrogen flame chromatograph.[20] The value of the cyclobutyl product differed slightly because we could only obtain a small amount of this minor isomer.

(20) Previous work from these laboratories has shown that flame ionization detector response values are similar from structural isomers if their retention times do not differ greatly: see G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold, and D. E. Williamson, *J. Org. Chem.*, **38**, 4109 (1973).

Free-Radical Reactions of Pentafluorobenzenesulfenyl Chloride with Alkanes and Alkylbenzenes

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Light-induced, free-radical reactions of pentafluorobenzenesulfenyl chloride with methylbenzenes give very high yields of pentafluorophenyl benzyl sulfides. With other alkylbenzenes which contain benzylic hydrogens, high yields of benzylic sulfides are also obtained along with small quantities of nonbenzylic pentafluorophenyl aralkyl sulfides. In all of these reactions, minor amounts of chloroalkylbenzenes and bis(pentafluorophenyl) disulfide are also obtained. In reactions with several alkanes, the major products are usually pentafluorophenyl alkyl sulfides, but substantial yields of chloroalkanes and bis(pentafluorophenyl) disulfide are also obtained.

In the past few years, sporadic reports of free-radical reactions of sulfenyl halides with hydrocarbons have been published. The studies to date, which primarily involve reactions of highly halogenated alkanesulfenyl chlorides[2,3] and pentachlorobenzenesulfenyl chloride,[4,5] show that the course of these reactions is highly sensitive to the nature of the organic group of the sulfenyl chloride. For example, the reactions of CF_3SCl[2] and Cl_3CSCl[3] with alkanes contrast sharply: only chloroalkanes are derived from the alkane in the Cl_3CSCl reactions, while in the CF_3SCl reactions trifluoromethyl alkyl sulfides are often the major products. In the few reactions of pentachlorobenzenesulfenyl chloride examined, sulfides were also major products.[4,5] This paper summarizes a study of the free-radical substitution reactions of pentafluorobenzenesulfenyl chloride (**1**) with alkylbenzenes and alkanes.

Results

The results of the experiments are summarized below and are tabulated in Table I. Authentic samples of several of the sulfide products were prepared by the UV-initiated addition of pentafluorobenzenethiol to appropriate olefins (Table II). Characterization of new compounds is given in Tables IV and V.[6]

Alkylbenzenes. The light-induced reactions of **1** with excess methylbenzenes, e.g., toluene, *o*-xylene, *p*-chlorotoluene, and mesitylene, are long chain free-radical reactions which give very high yields of pentafluorophenyl benzyl sulfides (**2–5**, Table I) and HCl, along with very low yields of bis(pentafluorophenyl) disulfide (**6**) and α-chlorotoluenes. For example, the reaction with toluene gave pentafluorophenyl benzyl sulfide (**2**) in over 95% yield (eq 1).

$$\underset{\mathbf{1}}{C_6F_5SCl} + CH_3C_6H_5 \xrightarrow{h\nu} \underset{\mathbf{2}}{C_6F_5SCH_2C_6H_5} + HCl + \underset{\mathbf{6}}{(C_6F_5)_2S_2} + ClCH_2C_6H_5 \quad (1)$$

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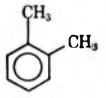
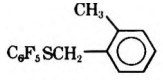
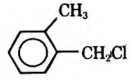
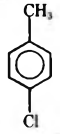
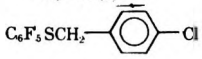
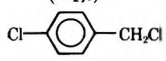
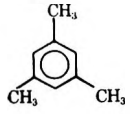
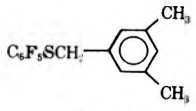
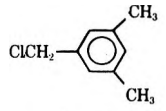
Table I. Photoreactions of C_6F_5SCl (1) with Hydrocarbons

Hydrocarbon		Registry no.	C_6F_5SCl, g, (mol)	Hydrocarbon/ C_6F_5SCl	Irradiation time, min	Yield of $(C_6F_5)_2S_2$, %	Sulfide (S) (yield)	Registry no.	Chloride (Cl) (yield)	S/Cl	Other products	Remarks
$C_6H_5CH_3$	75 mL 65 g 0.705 mol	108-88-3	10.08 (0.0429)	16.4	30	~1	$C_6F_5SCH_2C_6H_5$ **2** (>95%)	33288-16-3	$C_6H_5CH_2Cl$ (trace)	>100:1	2 unknown traces	
	100 mL 90 g 0.845 mol	95-47-6	16.31 (0.0695)	12.1	25	3–5	 **3** (~95%)	65015-48-7	 (~1%)	100:1	2 unknown traces	Yield of distilled sulfide **3** = 82%
	60 mL 64 g 0.507 mol	106-43-4	4.0 (0.0171)	29.7	73	<10	 **4** (>90%)	65015-49-8	 (few %)		2 unknown traces	
	60 mL 52 g 0.431 mol	108-67-8	4.54 (0.0193)	22.3	30	<10	 **5** (>90%)	65015-50-1	 (few %)		Unknown trace	Sulfide **5** crystallized after excess mesitylene was distilled
$C_6H_5CH_2$-CH_3	67 mL 58.1 g 0.547 mol	100-41-4	9.70 (0.0413)	13.2	15	2–4	$C_6F_5SCH(CH_3)$-C_6H_5 **7** (94–95%)	65015-51-2	$C_6H_5CHClCH_3$ (1–2%)	50–100:1	Unknown trace	Yield of distilled sulfides **7** and **8** > 80%
							$C_6F_5SCH_2CH_2$-C_6H_5 **8** (~3%)	65015-52-3	$C_6H_5CH_2CH$ (trace)			
C_6H_5CH-$(CH_3)_2$	50 mL 43.2 g 0.359 mol	98-82-8	7.00 (0.0298)	12.0	17	1–2	$C_6F_5SC(CH_3)_2$-C_6H_5 **9** (91%)	65015-53-4	$C_6H_5C(CH_3)_2$-Cl	~50:1	Traces of α-methylstyrene + several unknowns	Sulfide **9** crystallized after excess cumene was distilled
							$C_6F_5SCH_2CH$-$(CH_3)C_6H_5$ **10** (8%)	65015-54-5	$C_6H_5CH(CH_3)$-CH_2Cl (1–2%)			
C_6H_5C-$(CH_3)_3$	60 mL 52.0 g 0.388 mol	98-06-6	10.00 (0.0426)	9.1	83	24	$C_6F_5SCH_2C$-$(CH_3)_2C_6H_5$ **11** (76%)	65036-37-5	$C_6H_5C(CH_3)_2$-CH_2Cl (8%)	9.5	Traces of C_6F_5Cl + several unknowns	Distillation yielded fraction boiling at 85–88 °C (0.5 mm) which solidified; recrystallization from CH_3OH gave **11** as needles
$(C_6H_5)_2$-CH_2	97 mL 97.1 g 0.577 mol	101-81-5	10.00 (0.0426)	13.5	161	10–20	C_6F_5SCH-$(C_6H_5)_2$ **12** (~70%)	65015-55-6	$ClCH(C_6H_5)_2$ (10–20%)			The sulfide **12**, which crystallized after the excess diphenylmethane was distilled, was isolated in 50% yield
c-C_6H_{12}	75 mL 58.4 g 0.694 mol	110-82-7	9.96 (0.0425)	16.3	40	32.4	c-$C_6H_{11}SC_6F_5$ **13** (67.6%)	56717-64-7	c-$C_6H_{11}Cl$ (15.2%)	4.45		Distillation through a small spinning band still did not cleanly separate **13** from disulfide

n-C_4H_{10}	75 mL 60 g 1.03 mol	106-97-8	20.00 (0.0852)	12.1	400	38.6	n-$C_4H_9SC_6F_5$ **15** (15.9%) $C_6F_5SCH(CH_3)$-C_2H_5 **16** (45.6%)	33288-22-1 65015-56-7	n-C_4H_9Cl (2.8%) $CH_3CHClC_2H_5$ (5.8%)	5.63 7.92	Traces of C_6F_5Cl and two pentafluorophenyl chlorobutyl sulfides
$(CH_3)_3CH$	24 mL 19.2 g 0.33 mol mol	75-28-5	1.00 mL 1.68 (0.00716)	46.1	70	40.4	$C_6F_5SCH_2CH$-$(CH_3)_2$ **17** (20.2%) $C_6F_5SC(CH_3)_3$ **18** (39.3%)	65015-57-8 65015-58-9	$ClCH_2CH$ $(CH_3)_2$ (0.4%) $ClC(CH_3)_3$ (6.1%)	47.05 6.49	Isobutylene and small quantity of a pentafluorophenyl chlorobutyl sulfide
$(CH_3)_2CH$- $CH(CH_3)_2$	65 mL 43 g 0.50 mol	79-29-8	10.0 (0.0426)	11.7	75	54.5	$C_6F_5SC(CH_3)_2$-$CH(CH_3)_2$ **19** (45.4%) $C_6F_5SCH_2CH$-$(CH_3)CH$-$(CH_3)_2$ **20** (trace)	65015-59-0 65015-60-3	$(CH_3)_2CClCH$-$(CH_3)_2$ (20%)	2.27	C_6F_5Cl (trace), detected by MS–GC

[a] Registry no.: C_6F_5SCl (1), 27918-31-6.

Table II. Free-Radical Additions of C_6F_5SH[a] to Olefins: $C_6F_5SH + C{=}C \xrightarrow{h\nu} C_6F_5SCCH$

Olefin		Registry no.	C_6F_5SH, g (mol)	Olefin/ C_6F_5SH	Irradiation time, min	Products (yield)	Remarks
$C_6H_5CH{=}CH_2$	12 mL 10.91 g 0.105 mol	100-42-5	10.00 (0.050)	2.1	195	$C_6F_5SCH_2CH_2C_6H_5$ **8** (80%)	
$C_6H_5C(CH_3){=}CH_2$	15 mL 13.7 g 0.116 mol	98-83-9	10.00 (0.050)	2.32	230	$C_6F_5SCH_2CH(CH_3)C_6H_5$ **10** (80%)	
	35 mL 28.4 g 0.343 mol	110-83-8	8.00 (0.040)	8.6	390	c-$C_6H_{11}SC_6F_5$ **13** (60%) + $C_6F_5SSC_6F_5$ (few %)	
$CH_2{=}CHCH_2CH_3$	30 mL 24 g 0.428 mol	106-98-9	10.00 (0.050)	8.6	320	$C_6F_5SCH_2CH_2CH_2CH_3$ **15** + $C_6F_5SSC_6F_5$	Gas chromatogram showed presence of much unreached thiol
$CH_3CH{=}CHCH_3$ (cis)	25 mL 20 g 0.357 mol	590-18-1	10.00 (0.050)	7.1	825	$C_6F_5SCH(CH_3)CH_2CH_3$ **16** + $C_6F_5SSC_6F_5$ sulfide/disulfide ratio 3:1	Gas chromatogram showed conversion was about 20%
$CH_2{=}C(CH_3)_2$	30 mL 19.8 g 0.353 mol	115-11-7	8.00 (0.04)	8.8	293	$C_6F_5SCH_2CH(CH_3)_2$ **17** (85–90%) + $C_6F_5SSC_6F_5$ (5–7%)	
$CH_2{=}C(CH_3)CH(CH_3)_2$	20 mL 13.6 g 0.16 mol	563-78-0	10.00 (0.05)	3.2	127	$C_6F_5SCH_2CH(CH_3)CH(CH_3)_2$ **20** (>90%) + $C_6F_5SSC_6F_5$ (few %)	

[a] Registry no.: C_6F_5SH, 771-62-0.

Table III. Ratio of Pentafluorophenyl Cyclohexyl Sulfide (S) and Chlorocyclohexane (Cl) Formed at Various Conversions in the Photoreaction of 1 with Cyclohexane: Analysis by Gas Chromatography

Sample no.	Time,[a] min	Conversion,[b] %	S/Cl[c]	S/Cl[d]
2	2	31	6.68	5.84
3	5	52	7.08	5.94
4	7.75	83	6.45	5.93
5	11	>95	6.83	6.62
6	16	100	6.97	6.44

[a] Time elapsed after light was turned on. [b] Conversion was estimated from the area of the peak for the product (**14**) of the dark reaction of excess 1 and *p*-methylacetophenone. [c] These ratios were determined from peak areas calculated from the product of the peak heights and the widths at half-height. [d] These ratios were determined by weighing the cut-out peaks traced onto thick, translucent paper.

With alkylbenzenes containing hydrogens on carbons both α and β to the benzene ring, both possible sulfides were obtained, with that derived by substitution on the α-carbon predominating. Thus, from ethylbenzene, **7** and **8** in a ratio of 30:1 were the major products. With cumene, again the major products were sulfides **9** and **10** in a ratio of 10:1. Low yields of **6**, α- and β-chlorocumene, and α-methylstyrene were also obtained.[7] Both of these were long chain reactions.

$C_6F_5SCH(CH_3)C_6H_5$ (**7**) $C_6F_5SCH_2CH_2C_6H_5$ (**8**)

$C_6F_5SC(CH_3)_2C_6H_5$ (**9**) $C_6F_5SCH_2CH(CH_3)C_6H_5$ (**10**)

The reactions with *tert*-butylbenzene, the only case examined of an alkylbenzene with no benzylic hydrogens, and diphenylmethane appeared to be slower than the reactions just discussed. The respective sulfides (**11** and **12**) were the major products, but much higher yields of **6** and the chlorides were obtained than were seen in the reactions discussed above.

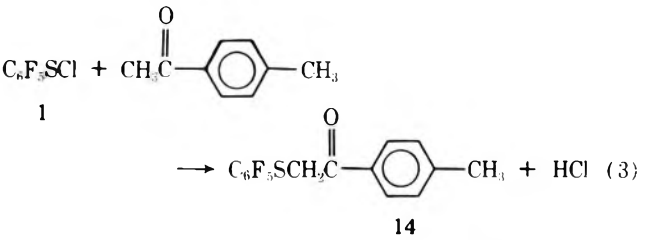
$C_6F_5SCH_2C(CH_3)_2C_6H_5$ (**11**) $(C_6H_5)_2CHSC_6F_5$ (**12**)

Alkanes. Light-induced reactions of 1 with excess cyclohexane, *n*-butane, isobutane, and 2,3-dimethylbutane did not appear to be as rapid as the reactions with methylbenzenes. In all cases but one, the highest yield products were pentafluorophenyl alkyl sulfides, but the yields of **6** and chlorohydrocarbons were much higher than in the methylbenzene reactions (Table I). The distributions of products in the cyclohexane, *n*-butane, and isobutane reactions were similar to those reported previously for the analogous reactions of pentachlorobenzenesulfenyl chloride,[5] except that in the reactions of 1 with *n*-butane and isobutane, chlorobutyl sulfides were also obtained, and in the isobutane reaction, isobutylene[10] was formed, all in very small yields.

In one experiment, a cyclohexane reaction (eq 2) was sampled periodically to detect any variation in the relative

$$\underset{\mathbf{1}}{C_6F_5SCl} + c\text{-}C_6H_{12} \xrightarrow{h\nu} \underset{\mathbf{13}}{c\text{-}C_6H_{11}SC_6F_5} + c\text{-}C_6H_{11}Cl + (C_6F_5)_2S_2 + HCl \quad (2)$$

amounts of the sulfide **13** and chlorocyclohexane during the course of the reaction. Each withdrawn aliquot was treated with excess *p*-methylacetophenone in order to convert unreacted 1 to a material (**14**) which gave a reproducible gas chromatography (GC) peak (eq 3). The GC analysis showed a small increase in the ratio of **13** to chlorocyclohexane between 30 and 100% conversion of 1 (Table III). In another cyclohexane experiment in which a 1:1 molar mixture of 1 and **6** in an excess of cyclohexane was irradiated until 1 was consumed, the GC ratio of **13** to chlorocyclohexane at the end of the experiment was 7.38, compared to 6.31 for an analogous experiment with no added **6**.



(3)

14

From the reaction with 2,3-dimethylbutane, the main products were pentafluorophenyl 1,1,2-trimethylpropyl sulfide (**19**), 2-chloro-2,3-dimethylbutane, and **6**. A trace amount of the other possible sulfide (**20**) was also obtained, but none of the corresponding chloroalkane, i.e., 1-chloro-2,3-dimethylbutane, was detected.

$C_6F_5SC(CH_3)_2CH(CH_3)_2$ (**19**) $C_6F_5SCH_2CH(CH_3)CH(CH_3)_2$ (**20**)

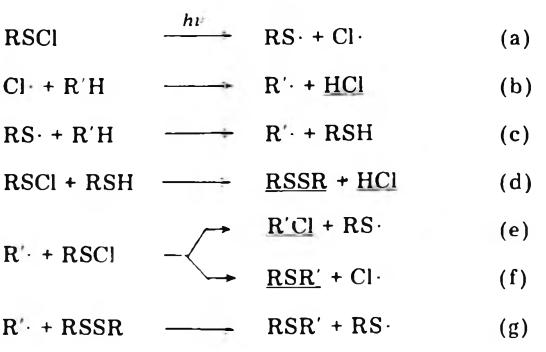
Discussion

In free-radical reactions of S–Cl compounds with hydrocarbons studied to date, the fate of the chain-carrying alkyl radicals has varied from exclusive C–S bond formation, e.g., in the reaction of SCl_2 with cyclohexane,[12] to exclusive C–Cl bond formation in the trichloromethanesulfenyl chloride reactions referred to above.[3] All other cases so far studied, including the reactions of 1, fall between these two extremes, giving both chloride and sulfide from the alkyl radical.

The steps in Scheme I have been proposed as the principal sources of the major products of sulfenyl halide–hydrocarbon free-radical reactions.[2,4,5] There is agreement that step e is the primary source of chlorohydrocarbon, but both steps f and g have been proposed to account for sulfide formation. If step f was the sole pathway for forming sulfide, then the ratio of sulfide to chlorohydrocarbon should remain constant throughout the reaction since both products would derive from a single substrate. It is apparent in the cyclohexane reaction examined in this study that some sulfide is being formed by a process other than step f (presumably step g) since the sulfide/chloride ratio increases somewhat as the reaction goes on (Table III). But since the increase is small, it is concluded that step g does not contribute importantly to sulfide formation. The same conclusion is drawn from the cyclohexane experiment done in the presence of a molar equivalent of **6**; the moderately higher sulfide/chloride ratio observed at the end of the reaction suggests relatively small involvement of step g.

Results of a previous study of free-radical reactions of

Scheme I



CF_3SCl with a group of alkanes show that the preference of attack by various alkyl radicals on sulfur vs. chlorine is best ordered on a steric basis, assuming that alkyl radicals intrinsically prefer to attack sulfur, but increasingly settle for attack on the more accessible chlorine as they become more bulky.[2] The same trend is evident in the reactions of 1 with alkyl radicals (Table I), but the shift to preference for chlorine by the more bulky radicals appears to be less pronounced than in the CF_3SCl reactions. The extremely high preference for attack on sulfur by benzylic radicals suggests that factors other than steric, e.g., reactivity of the radical, can be important in determining the pattern of attack by hydrocarbon radicals upon sulfenyl chlorides.

Experimental Section

I. Free-Radical Reactions of 1 with Hydrocarbons. A stirred solution of 1 dissolved in excess hydrocarbon contained in a quartz tube (7 × 1.5 in.) was irradiated under nitrogen with a sunlamp until the characteristic color of 1 was gone and the evolution of gas ceased. The reaction mixture was analyzed quantitatively by gas chromatography, and the principal products were identified by (1) comparison of retention times with materials of known structure, (2) mass spectroscopic examination of peaks in the gas chromatogram, or (3) isolation by distillation followed by elemental and proton NMR analyses. Details of the experiment are tabulated in Table I. Characterization of all new compounds is given in Tables IV and V.[6]

II. Free-Radical Reactions of Pentafluorobenzenethiol with Olefins. A stirred solution of the thiol and olefin contained in a quartz tube (7 × 1.5 in) fitted with a dry ice condenser and a magnetic stirrer was irradiated under nitrogen with a spiral-shaped, low-pressure mercury resonance lamp fitted around the reactor. The adducts were isolated by distillation, and structures were established by ^1H NMR spectroscopy. The details of these reactions are tabulated in Table II.

III. Determination of the Ratio of Pentafluorophenyl Cyclohexyl Sulfide (13) to Chlorocyclohexane at Various Conversions in the Photoreaction of 1 with Cyclohexane. A solution of 2.0 mL of 1 and 30 mL of cyclohexane (both freshly distilled) was placed in a small Pyrex flask fitted with a magnetic stirrer, a reflux condenser, and a syringe adapter. The mixture was irradiated with a sunlamp placed 5–6 in from the reactor. Samples (0.5 mL) were withdrawn periodically via syringe. Each sample was placed in a test tube containing 0.2 mL of *p*-methylacetophenone and shaken until colorless. A 5-μL sample was then examined by GC. The results of the measurements are given in Table III.

IV. Reaction of 1 with *p*-Methylacetophenone. A 5-mL amount of 1 was added in small portions to 80 mL of freshly distilled *p*-methylacetophenone with stirring. The color of 1 faded quickly after each addition. GC analysis showed the presence of one product. Distillation through a small Vigreux still gave 8.40 g (70%) of pentafluorophenyl *p*-methylphenacyl sulfide (14), distilling at 116–122 °C (0.20 mm). Elemental analysis and a ^1H nmr spectrum data are given in Tables IV and V.[6]

V. Reaction of 1 with Cyclohexane in the Presence of 6. A mixture of 0.2 mL (0.31 g, 0.00132 mol) of 1, 0.53 g (0.00133 mol) of 6, and 3 mL of cyclohexane was irradiated as described above for 21 min. The color of the reaction mixture remained pale yellow during the last 5 min of the irradiation period. The mixture was analyzed by GC, and the ratio of the peak areas corresponding to 13 and chlorocyclohexane was found to be 7.38 (average of two determinations).

For comparison, a mixture of 0.2 mL of 1 and 3 mL of cyclohexane was similarly irradiated for 13 min, after which the mixture was essentially colorless. The peak area ratio of 13 to chlorocyclohexane was found to be 6.31.

VI. Preparation of 1. Compound 1 was prepared by the chlorination of pentafluorobenzenethiol (Peninsular Chem. Research) in carbon tetrachloride as described by Sheppard and Foster.[13]

VII. Gas Chromatography. The GC analyses were done primarily with a 6 ft × 0.25 in column packed with 20% SE-30 on 60–80 mesh WAWDMCS. Temperatures varied from 50 to 200 °C. The helium flow rate was about 100 mL/min.

VIII. Mass Spectroscopy/Gas Chromatography. A Du Pont Model 21-490 mass spectrometer interfaced to a Varian Model 1440 gas chromatograph and a VG 2040 data system was used.

Registry No.—14, 65015-61-4; *p*-methylacetophenone, 122-00-9.

Supplementary Material Available: Tables IV and V of elemental analyses and ^1H NMR spectral data for the new pentafluorophenyl alkyl and aralkyl sulfides (8 pages). Ordering information is given on any current masthead page.

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Peracid Oxidations of Cyclopropenes and Cyclopropenones[1a]

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The reactions of cyclopropenes **1a–c** with peracid yield isomeric conjugated ketones **2a–c** and **3a,b**. These conversions are interpreted in terms of an oxabicyclobutane intermediate. The peracid oxidation of cyclopropenones 11 and 21 were shown to initially produce CO_2 and an acetylene. The latter is converted to other products under the reaction conditions.

Considerable recent effort has been directed toward the synthesis and chemical characterization of novel small-ring heterocyclic systems. 2-Oxabicyclo[1.1.0]butane is the parent of one such class of highly strained heterocycles. Although no authentic example of this elusive structure has yet been described in the literature, species of this type have been considered as reactive intermediates in photochemical isomerizations of conjugated carbonyl compounds[2] and from peracid oxidations of cyclopropenes.[3–8] In this report, we detail our results concerning potential approaches to oxabicyclobutanes.

Concurrently with published studies, we too have explored the peracid oxidation of cyclopropenes. Thus, oxidation of 1,2-diethyl-3-carbethoxycyclopropene (**1a**) with an excess of

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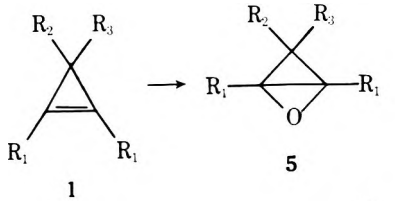
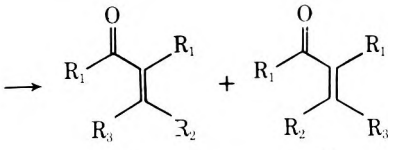
m-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 solution resulted in an 85:15 mixture of isomeric conjugated enones **2a** and **3a**. The use of methanol as solvent gave a 91:9 ratio of **2a/3a**, whereas a 90:10 mixture was obtained in cyclohexane. However, neither peracetic acid nor peroxybenzimidic acid[9] promoted appreciable conversion of **1a**. The structures of the enones follow from their spectral characteristics which are detailed in the Experimental Section. The NMR data permit assignments of double-bond configurations, since the olefinic proton should be at lower field for the *E* isomer relative to the *Z* form.[10] The isomeric relationship of **2a** and **3a** was readily confirmed by photochemical equilibration. However, these enones did not interconvert under the reaction conditions, indicating that the observed ratios reflect kinetic product distributions.

The reaction of **1b** (in which a hydroxymethyl group is present at C-3) with MCPBA in CH_2Cl_2 produced a 65:35 mixture of **2b** and **3b**. In methanol the product ratio was 70:30 and in cyclohexane it was 60:40. Product stereochemistry is again assigned by NMR. Photoequilibration experiments interrelated the two enones, which were stable to interconversion under the reaction conditions.

Sterically hindered cyclopropene **1c** was examined with the idea that its bulky substituents might permit the isolation of an unstable intermediate. This strategy has been successfully employed in a number of similar situations. However, in the case of **1c** only conjugated ketone **2c** was produced by MCPBA oxidation, even when the reaction product was examined at 0 °C. Since certain hindered olefins are epoxidized by ozone,[11] the ozonolysis of 1,2,3-tri-*tert*-butylcyclopropene (**1d**) was studied at low temperatures in the absence of protic materials. Unfortunately, diketone **4**, derived from normal ozone double-bond cleavage, was the only important product.

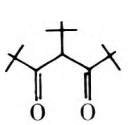


1 **5**



2 **3**

a, R_1 = Et; R_2 = CO_2Et; R_3 = H
b, R_1 = Et; R_2 = CH_2OH; R_3 = H
c, R_1 = *t*-Bu; R_2 = R_3 = Me
d, R_1 = R_2 = *t*-Bu; R_3 = H
e, R_1 = Ph; R_2 = CH_2OH; R_3 = H
f, R_1 = Ph; R_2 = CH_2OMe; R_3 = H



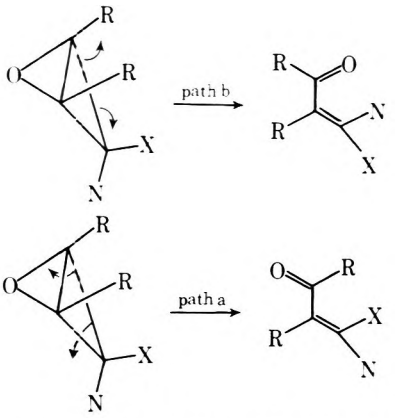
4

6

Although concrete evidence has still not been obtained for the intermediacy of oxabicyclobutanes **5** in the peracid oxidation of cyclopropenes, the production of conjugated carbonyl compounds is most readily rationalized in terms of the formation and spontaneous rearrangement of such species.[3-8] The latter transformation is formally analogous to the bicyclobutane–butadiene isomerization, which has received considerable attention.[12] If similar concerted mechanisms obtain in these structurally related systems, the proposed oxabicyclobutanes must be much more susceptible to thermal rearrangement than their hydrocarbon analogues. In fact, the isomerization of the parent oxabicyclobutane to acrolein is predicted[2,13] to be ca. 20 kcal/mol more exothermic than the bicyclobutane to butadiene conversion when equivalent strain energies are assumed for the two strained-ring systems.[14] Nonetheless, estimates of the expected kinetic behavior of oxabicyclobutane suggest that it might be an observable species.[13]

The heterocyclic system is more likely to react by acid-catalyzed mechanisms, but kinetic[8] and product studies[7] have been used to argue persuasively against intermediates of type **6** anywhere in the overall conversion of cyclopropenes to conjugated carbonyl compounds. However, protonation of oxabicyclobutanes could well hasten *concerted* decomposition to protonated enones.[4]

Friedrich has calculated that the parent oxabicyclobutane should display a preference for "disrotatory" over "conrotatory" ring opening.[4] He has also inferred from product studies on **1e** and **1f** that the disrotatory mode leading initially to a *transoid* enone conformer (path a) is preferred over the alternate disrotatory process which gives the *cisoid* enone (path b). [5]These transformations result in geometrical isomers of the enone product when $R_2 \neq R_3$ in oxabicyclobutane **5**. The above hypothesis does not appear to satisfactorily accommodate our results.



$\mathbf{5_X}$, X = R_2, N = H; $\mathbf{5_N}$, X = H, N = R_2

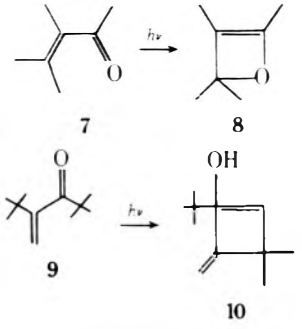
In order to follow the stereochemistry of the oxabicyclobutane ring opening, a knowledge of the structure of this reactive intermediate is required. In the case of **1a** this can be predicted to be predominately the exo isomer $\mathbf{5_X}$ with some confidence. This conclusion is based on the known stereochemistry of attack of other sterically demanding reagents on cyclopropenes[15] and the usual propensity for peracid to approach a cyclic olefin bearing a proximate ester function from the side of the molecule away from this polar group.[16] The rules given above predict **3a** as the major enone product from $\mathbf{5_X}$, whereas experimentally **2a** is observed to predominate. Note also that the **2a/3a** product ratio is not significantly different in the three solvents utilized (cyclohexane, CH_2Cl_2, and methanol).

The stereochemistry of the intermediate from **1b** is less certain, although there is ample precedence for expecting peracid attack cis to the hydroxymethyl group owing to association by hydrogen bonding prior to reaction.[16] This line of reasoning predicts preferential formation of the *endo*-oxabicyclobutane $\mathbf{5_N}$ in inert solvents. Rearrangement of $\mathbf{5_N}$ is predicted to yield **2b** as the major enone product in agreement with the experimental results. However, hydrogen bonding between peracid and **1b** will not be important in methanol and the exo intermediate $\mathbf{5_X}$ should predominate in this solvent. Accordingly, a reversal in the enone stereochemistry would be anticipated. In fact, the **2b/3b** product

distribution is not greatly affected by the nature of the solvent. Thus, either the neighboring hydroxy group is not functioning as anticipated or the product ratio is not dependent on the stereochemistry of the oxabicyclobutane intermediate. In any event, the predominance of the *E* enone for both **1a** and **1b** contrasts markedly with the results for the pair **1e** and **1f** which give major enones of opposite stereochemistry (*Z* and *E*, respectively).

We conclude that the currently available data do not present a consistent pattern for the 2/3 ratios which can be rationalized in terms of a preferred decomposition mode for the intermediate oxabicyclobutanes. Rather, if such species are indeed formed, their product ratios are probably determined by subtle substituent interactions. In fact, typical product distributions correspond to rather similar energies for the competitive kinetic pathways to isomeric enone products; i.e., the reactions are not very stereoselective.

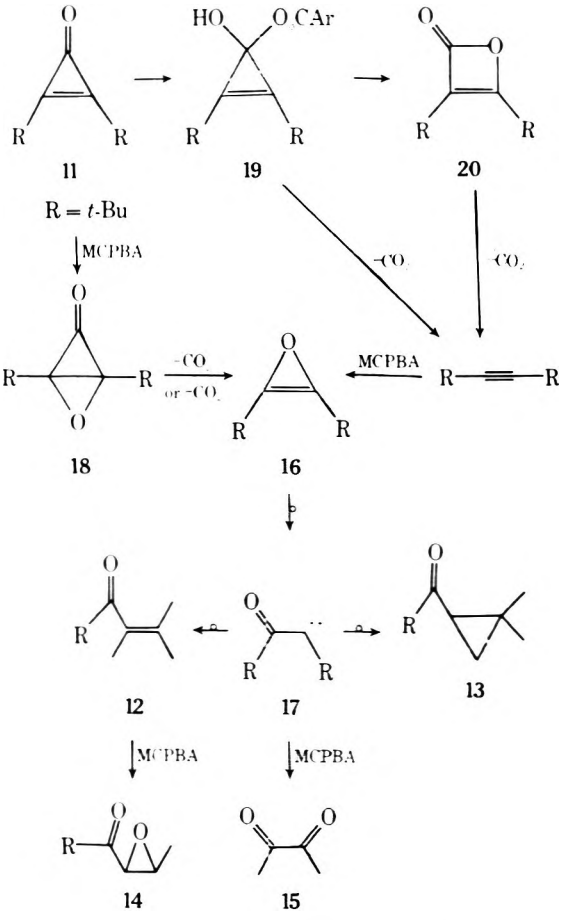
The possibility of photochemically isomerizing conjugated enones to oxabicyclobutanes has been considered. However, ketone **7** does not so react, preferring transformation to the isomeric oxetene **8** instead,[2] probably from a cisoid conformation of the starting enone. Consequently, the photochemistry of **9**, an enone which cannot readily achieve a planar cisoid conformation, was examined with the hope that the alternate cycloaddition mode to an oxabicyclobutane might be favored by this conformational distortion. No reaction was observed upon prolonged irradiation of **9** through Pyrex, but a facile photoconversion occurred upon irradiation through quartz. Disappointingly the photoisomer thus obtained was shown to be cyclobutanol **10**. Such photochemical transformations are, of course, amply precedented.[17]



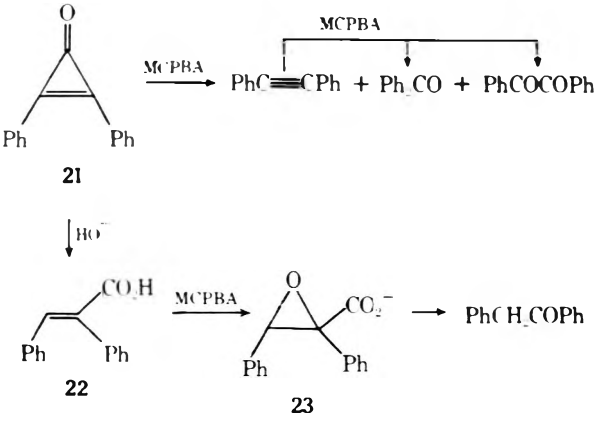
Peracid oxidations were also performed on several cyclopropenones, a rather special class of cyclopropenes.[15,18] Thus, di-*tert*-butylcyclopropenone (**11**) reacted slowly with an excess of MCPBA to yield di-*tert*-butylacetylene and ketones **12**, **13**, **14**, and **15** in a 1:2:5:90:2 ratio. One equivalent of CO_2 was also produced. The carbonyl products suggest the intermediacy of oxirene **16**, a highly reactive, antiaromatic species which is expected to yield stable products via the isomeric ketocarbene **17**.[19] A pathway to oxirene **16** proceeding by way of the oxabicyclobutanone **18** was considered prior to the identification of di-*tert*-butylacetylene as a minor product from **11**. However, the reaction of this acetylene with peracid is known to yield ketones **12**–**15** in a process postulated to involve the oxirene intermediate **16**.[19] Repeating the oxidation of the acetylene under the reaction conditions used for the cyclopropenone gave ketones **12**, **13**, **14**, and **15** in a 3:5:90:2 ratio. The identity of the product distributions in the two oxidation reactions establishes with virtual certainty that the acetylene is a key intermediate in the cyclopropenone reaction. Furthermore, this description is more in accord with the characteristic behavior of cyclopropenones, which are likely to suffer nucleophilic attack at the carbonyl group.[16] Adduct **19**, formed by addition of peracid to cyclopropenone **11**, can fragment to CO_2 and di-*tert*-butylacetylene either concertedly or by first rearranging to lactone **20**. Cyclopropanones are reputed to undergo a related conversion to olefin and CO_2.[20]

Acetylenes are also produced as side products during the peracid oxidation of certain highly hindered cyclopropenes by a process which appears to involve an intermediate cyclopropenyl cation.[7] (Interestingly cyclopropenone **11** did not react with ozone, an electrophilic reagent.)

The MCPBA oxidation of diphenylcyclopropenone (**21**) resulted in a 40:10:50 mixture of diphenylacetylene, benzophenone, and benzil. Identical treatment of the acetylene resulted in partial conversion to the two ketones in a 1:5 ratio, essentially as described in the literature.[21] An intermediate oxirene is again postulated as the key intermediate.

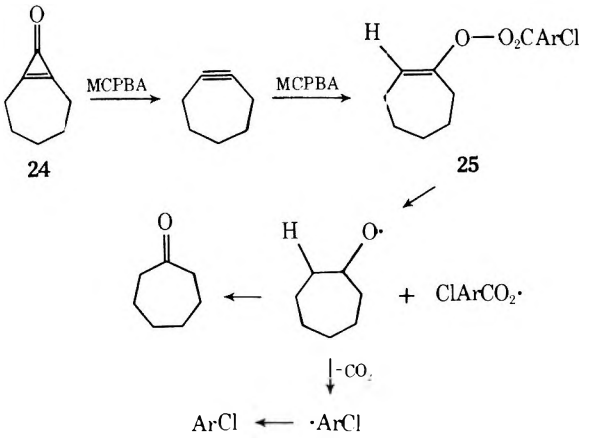


The absence of benzyl phenyl ketone in the product mixture from **21** and MCPBA was puzzling in view of a report that the oxidation of **21** with basic hydrogen peroxide gave this ketone as the major product.[22] In fact, duplication of this experiment led to a 30:10:40:20 mixture of diphenylacetylene, benzophenone, benzil, and benzyl phenyl ketone more in agreement with the MCPBA results. Submitting cyclopropanone **19** to the basic reaction conditions in the absence of hydrogen peroxide gave *cis*-1,2-diphenylacrylic acid **22** as anticipated.[23]



Acid **22** was readily converted to benzyl phenyl ketone in high yield by basic hydrogen peroxide. These results account for the experimental discrepancies and demonstrate part of the route to this ketone. The salt of acid **22** is undoubtedly epoxidized to give the glycidic acid salt **23** which decarboxylates to benzyl phenyl ketone.

Finally, cycloheptenocyclopropenone (**24**) was transformed by excess MCPBA to a complex mixture containing a 51% yield of chlorobenzene and 6% of cycloheptanone as the major components. These unanticipated results were not further investigated, but the observed products can be rationalized in terms of initial acetylene formation. In this instance, the very unstable cycloheptyne is postulated to nucleophilically add peracid to give the vinyl perester **25** which can proceed to the observed products by plausible free-radical processes.



Experimental Section

General. NMR spectra were recorded for CCl_4 solutions on a Varian HR-220 spectrometer; infrared spectra were obtained on a Perkin-Elmer IR-7 prism spectrophotometer. Commercial *m*-chloroperbenzoic acid was recrystallized from CH_2Cl_2 after which it analyzed as >98% peracid.[24] Sodium sulfate was used as a drying agent. Analyses were performed by Spang Microanalytical Laboratory.

1,2-Diethyl-3-carbethoxycyclopropene (1a). To a mixture of 10 g of 3-hexyne and 0.1 g of electrolytic Cu at reflux temperature was added 50 g of ethyl diazoacetate over a 12-h period. After gas evolution ceased, the mixture was distilled to give 7.5 g (55%) of 1,2-diethyl-3-carbethoxycyclopropene of >95% purity by GLPC: bp 90–95 °C (30 mm); IR 5.28, 5.81, 7.35, 8.10, and 8.48 μm; NMR δ 1.14 (t, 6, J = 7 Hz), 1.19 (t, 3, J = 7 Hz), 1.96 (s, 1), 2.42 (q, 4, J = 7 Hz), and 4.01 (q, 2, J = 7 Hz).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.2; H, 9.5.

Peracid Oxidation of 1a. A mixture of 0.5 g of **1a** and 2 g (4 equiv) of MCPBA in 25 mL of CH_2Cl_2 was stirred at 0 °C for 3 h, washed successively with solutions of $NaHCO_3$, $NaHSO_5$, $NaHCO_3$, and dried. Solvent removal under vacuum at 0 °C gave 2.1 g (96%) of a mixture of two products in a 85:15 ratio by GLPC. Inspection of the crude reaction mixture by NMR indicated that the GLPC isolated products were the only components. The major component was ethyl (*E*)-3-ethyl-4-keto-2-hexenoate (**2a**): IR 5.80, 5.92, 6.11, and 8.28 μm; NMR δ 0.98 (t, 3, J = 7 Hz), 1.09 (t, 3, J = 7 Hz), 1.29 (t, 3, J = 7 Hz), 2.63 (q, 2, J = 7 Hz), 2.75 (q, 2, J = 7 Hz), 4.17 (q, 2, J = 7 Hz), and 6.33 (s, 1).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.3; H, 8.9.

The minor component was ethyl (*Z*)-3-ethyl-4-keto-2-hexenoate (**3a**); IR 5.82 (br), 6.08, 8.3, and 8.8 μm; NMR δ 1.10 (br t, 6, J = 7 Hz), 1.25 (t, 3, J = 7 Hz), 2.51 (br q, 2, J = 7 Hz), 2.57 (q, 2, J = 7 Hz), 4.11 (q, 2, J = 7 Hz), and 5.56 (t, 1, J = 2 Hz).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.3; H, 8.7.

Reaction of **1a** with peracetic acid at 0 °C for 24 h resulted in recovery of starting material, as did reaction with peroxybenzimidic acid.[9]

Peracid Oxidation of 1a in Methanol. A mixture of 0.5 g of **1a** and 2 g (4 equiv) of MCPBA in 25 mL of methanol was stirred at 0 °C for 6 h. Addition of 25 mL of CH_2Cl_2 and workup as described above gave **2a** (91%) and **3a** (9%).

Peracid Oxidation of 1a in Cyclohexane. A mixture of 0.5 g of **1a** and 2 g (4 equiv) of MCPBA in 25 mL of cyclohexane was stirred at 0 °C for 6 h. After workup as described above the solvent was removed under vacuum to give a 90:10 ratio of **2a/3a**.

Photoequilibration of 2a and 3a. Pure samples of **2a** and **3a** were independently irradiated in a Rayonet reactor with 3100-Å bulbs until an identical ratio of 91:9 of **2a/3a** was obtained (6 h).

Acid Stability of 2a and 3a. Pure samples of **2a** and **3a** were stirred with a mixture of 0.5 g of *m*-chlorobenzoic acid and 0.5 g of MCPBA in 25 mL of CH_2Cl_2 at 0 °C for 24 h. Workup as described above followed by GLPC analysis indicated no interconversion of isomers under these reaction conditions.

1,2-Diethyl-3-hydroxymethylcyclopropene (1b). To a slurry of 1 g of LAH in 100 mL of ether in an ice bath was added 1 g of **1a** in ether at a rate to maintain the temperature below 5 °C. Immediately after the addition of **1a**, 2 mL of saturated Na_2SO_4 solution was added slowly. Filtration and removal of solvent gave 0.5 g (66%) of **1b** which was 96% pure by GLPC: IR 3.05, 5.40, 6.9, and 9.9 μm; NMR δ 1.14 (t, 6, J = 7 Hz), 1.15 (t, 1, J = 7 Hz), 2.43 (q, 4, J = 7 Hz), 3.41 (d, 2, J = 7 Hz), and 4.20 (s, 1).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.0; H, 11.2.

Peracid Oxidation of 1b. A mixture of 1 g of **1b** and 2 g of MCPBA (1.5 equiv) in 20 mL of CH_2Cl_2 was stirred for 6 h in an ice bath. After workup the solvent was removed under vacuum at 0 °C to give 1.1 g (96%) of a mixture of two compounds in a 65:35 ratio. The major component was (*E*)-4-ethyl-6-hydroxy-4-hexen-3-one (**2b**): IR 2.98, 5.88, 6.10, and 8.05 μm; NMR δ 1.08 (t, 3, J = 7 Hz), 1.18 (t, 3, J = 7 Hz), 2.18 (q, 2, J = 7 Hz), 2.68 (q, 2, J = 7 Hz), 3.51 (d, 2, J = 6 Hz), 4.50 (s, 1), and 6.72 (t, 1, J = 6 Hz).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.3; H, 10.0.

The minor component was (*Z*)-4-ethyl-6-hydroxy-4-hexen-3-one (**3b**): IR 2.98, 5.89, 6.11, and 8.15 μm; NMR δ 1.03 (t, 3, J = 7 Hz), 1.20 (t, 3, J = 7 Hz), 2.20 (q, 2, J = 7 Hz), 2.70 (q, 2, J = 7 Hz), 4.31 (d, 2, J = 6 Hz), 4.73 (s, 1), and 5.65 (t, 1, J = 6 Hz).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.6; H, 9.8.

Oxidation using peracetic acid in an ice bath for 24 h resulted in recovery of starting material, as did oxidation with peroxybenzimidic acid.

Peracid Oxidation of 1b in Methanol. A mixture of 0.5 g of **1b** and 1 g of MCPBA (1.5 equiv) in 25 mL of methanol was stirred in an ice bath for 6 h. Addition of 25 mL of CH_2Cl_2 and processing as described above gave a **2b–3b** mixture in a 70:30 ratio (93%).

Peracid Oxidation of 1b in Cyclohexane. A mixture of 0.5 g of **1b** and 1 g (1.5 equiv) of MCPBA in 25 mL of cyclohexane was stirred at 0 °C for 6 h. After workup as described above the solvent was removed under vacuum to give a 60:40 ratio of **2b/3b**.

Photoequilibration of 2b and 3b. Pure samples of **2b** and **3b** were independently irradiated in a Rayonet reactor with 3100-Å bulbs until an identical cis–trans ratio of 27:73 was observed (3 h).

Acid Stability of 2b and 3b. Samples of pure **2b** and **3b** were stirred with 0.5 g of *m*-chlorobenzoic acid and 0.5 g of MCPBA in 25 mL of CH_2Cl_2 for 24 h in an ice bath. Workup and analysis as described above indicated no interconversion of isomers under these reaction conditions.

1,2-Di-*tert*-butyl-3,3-dimethylcyclopropene (1c). To 1 g of di-*tert*-butylcyclopropenone[25] in 50 mL of ether was added 10.4 mL of a 1.15 M MeLi solution. After stirring 2 h, 1 mL of water was added and stirring was continued for an additional 2 h. The solution was dried and 1 mL of 10% $HClO_4$ in acetic anhydride was added dropwise at 0°C. The solid thus formed was removed by filtration and washed with ether. To this material suspended in 100 mL of ether was added 10.4 mL of 1.15 M MeLi solution. After stirring 3 h, 1 mL of water was added, the ether solution was dried, and the solvent was removed to give 1,2-di-*tert*-butyl-3,3-dimethylcyclopropene (**1c**): IR 5.50, 7.19, 9.58, and 10.0 μm; NMR δ 0.98 (s, 6) and 1.21 (s, 18).

Anal. Calcd for $C_{13}H_{24}$: C, 86.59; H, 13.41. Found: C, 86.3; H, 13.7.

Peracid Oxidation of 1c. A mixture of 300 mg of **1c** and 600 mg (2 equiv) of MCPBA in 10 mL of CH_2Cl_2 was stirred at 0 °C for 2 h. The mixture was worked up in the usual fashion and the solvent was removed under vacuum at 0 °C to give 295 mg (90%) of 2,5,5-trimethyl-3-*tert*-butyl-2-hexen-4-one (**2c**), pure by GLPC: IR 5.91, 6.13, 7.18, 7.32, 9.56, and 10.0 μm; NMR δ 1.15 (s, 9), 1.21 (s, 9), 1.96 (s, 3), and 2.16 (s, 3).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.4; H, 12.4.

Reaction of 1,2,3-Tri-*tert*-butylcyclopropene[25] (1d) with Ozone. Into a solution of 172 mg of **1d** in 10 mL of CH_2Cl_2 at −78 °C

was bubbled 1 equiv of ozone from a Welsbach ozone generator. After bubbling nitrogen through the solution for 30 min, it was allowed to warm to room temperature. Removal of the solvent under vacuum gave a mixture of two compounds in a 90:10 ratio. The major compound isolated by GLPC (160 mg, 80%) was assigned as 2,2,6,6-tetramethyl-4-*tert*-butyl-3,5-heptadione, (**4**): IR 5.80, 10.0 μm; NMR δ 0.97 (s, 9), 1.14 (s, 18), and 4.55 (s, 1); mass spectrum *m/e* 57 (100), 85 (60), 128 (13), 141 (7), 156 (2), 169 (3), 183 (7), 184 (7), and 240 (2).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.6; H, 11.7.

Inspection of the reaction mixture by NMR at −78 °C indicated that 4 was already formed and no change was observed upon warming. A reaction under identical conditions in methanol solvent gave similar results.

4-*tert*-Butyl-2,2-dimethyl-4-penten-3-one (9). A 3-g sample of 2,2,5,5-tetramethyl-3,4-hexadione was treated with 12 mL of a 1.7 M methyllithium solution in 300 mL of ether at room temperature and stirred for 2 h. A 5-mL sample of acetyl chloride was added and stirring was continued for an additional 3 h. The reaction was quenched by the addition of 10 mL of water. The mixture was washed with water and a solution of $NaHCO_3$, and dried. The ether was removed by vacuum and the crude material passed through a flow system pyrolysis tube at 450 °C. The collected 4-*tert*-butyl-2,2-dimethyl-4-penten-3-one (**9**) was purified by GLPC and gave: IR 5.95, 6.17, 7.22, 7.38, 7.80, 8.31, 9.61, 10.0, 11.0, and 11.4 μm; NMR δ 1.13 (s, 9), 1.19 (s, 9), 5.02 (s, 1), and 5.25 (s, 1).

Photolysis of 9. A 50-mg sample of **9** was dissolved in 125 mL of pentane and irradiated through Pyrex at −78 °C with a Hanovia medium-pressure Hg arc. After 12 h the pentane was removed. The NMR of the residue indicated only starting material. Irradiation *through quartz* under the same conditions for 30 min gave three products by GLPC in a 96:2:2 ratio. Collection of the major product by GLPC and spectral analysis indicated 1-*tert*-butyl-3,3-dimethyl-2-methylenecyclobutanol (**10**): IR 2.80, 2.93, 6.05, 7.24, 7.32, 8.87, 10.4, 11.2, and 11.6 μm; NMR δ 0.92 (s, 9), 1.07 (s, 3), 1.24 (s, 3), 1.88 (AB, 2, $\Delta\nu$ = 0.4 ppm, J = 13 Hz), 1.75 (s, 1), 4.91 (s, 1), and 5.05 (s, 1).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.6; H, 12.0.

Peracid Oxidation of 11. A mixture of 1 g of **11** and 5.2 g of MCPBA (4.5 equiv) in 25 mL of CH_2Cl_2 was refluxed for 8 h. The usual workup gave 1.3 g of a mixture of 5 products in a 1:2:5:90:2 ratio by GLPC. The first product was identified as di-*tert*-butylacetylene by spectral comparison with an authentic sample.[26] The second product was identified as 2,3,5,5-tetramethyl-2-hexen-4-one (**12**) by GLPC retention time and mass spectral comparison with an authentic sample:[19] mass spectrum *m/e* 154 (9), 139 (8), 97 (87), 83 (45), 69 (22), and 57 (100). The third product was identified as 1,2,2-trimethylcyclopropyl *tert*-butyl ketone (**13**) by spectral comparison with an authentic sample.[27] The fourth product was identified as 2,3,5,5-tetramethyl-2,3-epoxy-4-hexanone (**14**) by spectral comparison with an authentic sample:[19] IR 5.91, 7.25, 7.31, 8.0, 11.4, and 12.0 μm; NMR δ 1.36 (s, 3), 1.29 (s, 3), 1.16 (s, 9), and 1.14 (s, 3); mass spectrum *m/e* 170 (19), 155 (40), 138 (1.5), 113 (15), 86 (62), 85 (46), 71 (57), and 57 (100). The fifth product was identified as 2,2,5,5-tetramethyl-3,4-hexadione (**15**) by spectral comparison with an authentic sample.

An identical experiment was conducted in which a slow stream of nitrogen was passed through the reaction mixture. The exiting gases were passed through $CaSO_4$ and a weighed drying tube containing Ascarite. The Ascarite gained 28.0 mg in weight which corresponds to a 97% yield of CO_2.

Peracid Oxidation of Di-*tert*-butylacetylene. A solution of 1 g of di-*tert*-butylacetylene was oxidized under the conditions described for di-*tert*-butylcyclopropenone to give **12, 13, 14,** and **15** in a 3:5:90:2 ratio by GLPC (94% total yield).

Reaction of 11 with Ozone. A solution of 1 g of **11** in 50 mL of CH_2Cl_2 at −78 °C was saturated with ozone from a generator until a blue color persisted. The color remained for 24 h, after which excess ozone was removed by passing through a nitrogen stream. Warming the reaction mixture to room temperature and removal of the solvent gave only recovered **19**.

Peracid Oxidation of Diphenylcyclopropenone (21). A mixture of 1 g of **21**[23] and 4.2 g (5 equiv) of MCPBA in 50 mL of CH_2Cl_2 was refluxed for 8 h. Usual workup gave 1.3 g of 40:10:50 mixture of diphenylacetylene, benzophenone, and benzil.

Hydrogen Peroxide Oxidation of 21. A mixture of 1 g of **21**, 0.5 g of NaOH, 2 mL of water, and 5 mL of 40% H_2O_2 in 25 mL of dioxane was stirred at room temperature for 24 h. The mixture was poured into 200 mL of water, acidified with 10% HCl, and extracted with ether. Drying and removal of the solvent gave a 30:10:40:20 mixture of diphenylacetylene, benzophenone, benzil, and benzyl phenyl ketone: mass spectrum *m/e* 196 (15), 178 (5), 165 (4), 105 (100), 92 (36), 78 (60), 51 (48), and 45 (42).

Reaction of 21 with Base. A mixture of 1 g of **21**, 0.5 g of NaOH, and 2 mL of water in 25 mL of dioxane was stirred for 24 h at room temperature. The mixture was poured into water, acidified with 10% HCl, and extracted with ether. Solvent removal gave crystalline *cis*-1,2-diphenylacrylic acid (**22**).[23]

Hydrogen Peroxide Oxidation of 22. A mixture of 0.5 g of **22**, 0.5 g of NaOH, 2 mL of water, and 5 mL of 40% H_2O_2 in 25 mL of dioxane was stirred at room temperature for 24 h. The mixture was poured into water, acidified with 10% HCl, and extracted with ether. Drying and removal of the solvent gave only benzyl phenyl ketone in 93% yield.

Peracid Oxidation of Cycloheptenocyclopropenone (24). A mixture of 1 g of **24**[28] and 5 g (3 equiv) of MCPBA in 50 mL of methylene chloride was stirred at reflux for 8 h. The usual workup gave a mixture of six products by GLPC in a 85:10:1:1:2:1 ratio. The major component was chlorobenzene (51% yield); the 10% product was cycloheptanone (6% yield based on starting cyclopropenone).

Registry No.—**1a,** 35920-11-7; **1b,** 65016-07-1; **1c,** 65016-08-2; **1d,** 23438-08-6; **2a,** 65016-09-3; **2b,** 65016-10-6; **2c,** 65016-11-7; **3a,** 65016-12-8; **3b,** 65016-13-9; **4,** 65016-14-0; **9,** 35373-26-3; **10,** 65016-15-1; **11,** 19985-79-6; **12,** 17325-92-7; **14,** 42915-86-6; **21,** 886-38-4; **24,** 696-47-9; ethyl diazoacetate, 623-73-4; methyllithium, 917-54-4; 2,2,5,5-tetramethyl-3,4 hexadione, 4388-88-9; di-*tert*-butylacetylene, 17530-24-4.

References and Notes

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Internal Rotation in *peri*-Phenylnaphthalenes[1]

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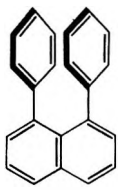
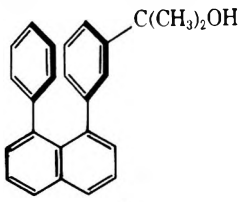
A 180° rotation about a phenyl–naphthyl bond is expected to be effectively blocked for derivatives of the *peri*-diphenylnaphthalenes, in which steric requirements force the phenyl rings to assume a face-to-face conformation. However, surprisingly low rotational energy barriers have been found. The preparation and the measurement of the barrier to phenyl ring rotation of a derivative of the highly crowded 1,4,5,8-tetraphenylnaphthalene system is described. The barrier for this substance is 14.9 kcal/mol compared with 16.4 kcal/mol determined for 1,8-diphenylnaphthalene; both of these barriers are much lower compared with the 33.5 kcal/mol reported for the stereotopically similar [3.4]paracyclophane. The differences are discussed in terms of a rotational transition state having large deformations of the naphthalene ring.

Molecular models suggest that the only possible geometry for 1,8-diphenylnaphthalene will have the phenyl rings face to face, **1**, and this has been confirmed by recent x-ray diffraction.[3] Even in this conformation there is severe crowding of the phenyl rings. As a result, the aryl rings would be ex-



1

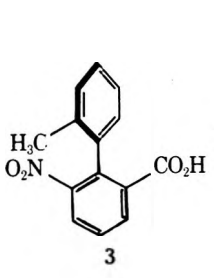
pected to have a high barrier to a 180° rotation about the aryl–naphthyl bond. Indeed, CPK space-filling models would seem to indicate that such a rotation is in fact impossible, except by breaking one or more bonds. House and co-workers have prepared several derivatives of 1,8-diphenylnaphthalene having a substituent at one meta position of each phenyl ring, with the expectation that they would be able to isolate cis and trans isomers.[4] However, it was not found possible to obtain separate isomers, and, instead, a single crystalline compound was isolated in each case. Subsequent NMR measurements[5] on the derivative, **2**, showed that the barrier to rotation was



2

only 16.4 kcal/mol, consistent with rapid rotation at room temperature.

The 1,8-diarylnaphthalenes may be profitably compared with the ortho-substituted biphenyls, for which many examples having rotational barriers high enough to allow separation of optical isomers are known, for example, **3** and **4**.[6] The naphthyl derivative, **5**, has also been resolved,[7] as has α,α′-binaphthyl, **6**, for which a rotational barrier of 22.5 kcal/mol was obtained.[8] Cram has reported that the [3.3]paracyclophane, **7**, showed no tendency to racemize at temperatures up to 240 °C[9] and that the [3.4]paracyclophane, **8**, racemized only



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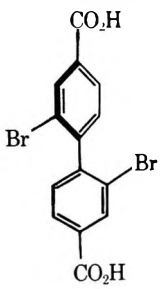

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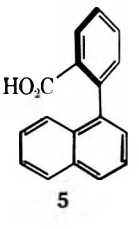

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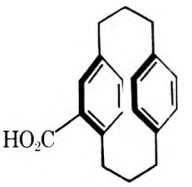

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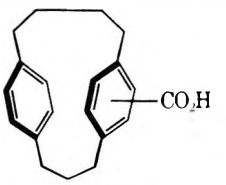
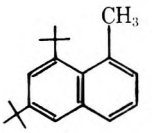


8

slowly at 160 °C.[10] The barrier to phenyl ring rotation in the latter was calculated to be 33.5 kcal/mol. These two compounds provide a striking contrast to derivatives of **1**, for which similar steric requirements would be inferred.

Several other naphthalene derivatives having different types of peri substituents have been recently reported to have what seem surprisingly low barriers to rotation about the naphthyl-substituent bond.[11,12] For example, the barrier to rotation of the *tert*-butyl group of **9** was <6 kcal/mol and that of **10** was estimated at about 6.5 kcal/mol.[11]



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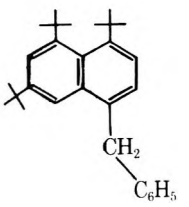
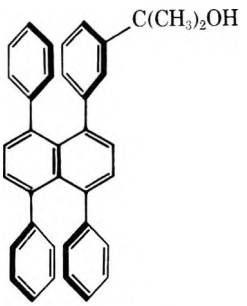


10

We report here the synthesis and measurement of the rotational barrier of the highly strained **11**, which has two sets of crowded *peri*-phenyl groups.



11

Synthesis and NMR Study of 11

The synthetic scheme for **11** had **12** as a key intermediate, with the *m*-chloro group intended to serve as a marker which

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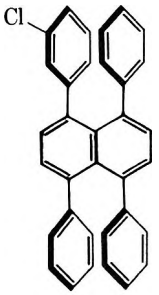
would be inert to conditions of the synthetic sequence, but which would permit direct functionalization of the aromatic ring after construction of the naphthalene framework. In-



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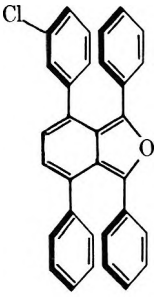


13

termediate **12** was synthesized in eight steps starting from *m*-chlorobenzaldehyde and involving preparation of the chlorotetraphenylbenzoisofuran, **13**, with subsequent Diels–Alder addition and aromatization, similar to the synthetic routes used previously in preparation of several substituted napthalenes including 1,4-diphenylnaphthalene,[13] 5,10-diphenylanthracene,[14] and 1,4,5,8-tetraphenylnaphthalene.[15]

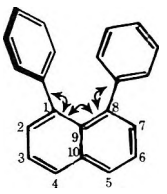
The chloro group of **12** proved to be highly inert, and standard procedures for generating the anion failed. Stirring with a solution of *n*-butyllithium gave no halogen–metal exchange. No reaction could be induced between **12** and strips of lithium metal and no reaction was observed when **12** was added to a freshly prepared dispersion of sodium. However, when **12** was added to an excess of fine lithium dust (140 mesh) under argon with bromobenzene present to activate the metal with ether as a solvent, the solution turned to a deep purple on heating to reflux. Addition of the organolithium compound to acetone in ether gave **11** in 57% yield.

When ring rotation of **11** is slow on the NMR time scale, its methyl groups become diastereotopic. The methyl proton NMR resonances of **11** at 100 °C were a single sharp peak, which, on lowering the temperature, broadened and at 5 °C began to separate into two equal signals. Visual matching using computer-generated spectra allowed calculation of the energy barrier for rotation, $\Delta G^{\ddagger}$, of 14.9 kcal/mol.[16]

The Rotational Mechanism of *peri*-Phenylnaphthalenes

Detailed calculations on the rotational barriers of some 2,2′-substituted biphenyls have been reported by Westheimer,[17] who showed that the rotational intermediates must have geometric deformations local to the interannular bond. Important distortions include bending of the ortho substituents away from each other, interannular bond stretching, and C–H (ortho) bond compression.

For *peri*-phenylnaphthalenes, a rotational transition state may be visualized in which one phenyl ring must turn to a position perpendicular to the adjacent *peri*-phenyl ring.[18] There are two modes of distortion available to the intermediate which we believe responsible for the low barriers observed. These two modes, which have no analogue in the biphenyls, are in-plane and out-of-plane splaying of the peri groups. In-plane splaying can occur both by a bending of the exocyclic naphthyl-substituent bond which increases the C9–C1-substituent angle and by an opening of the C1–C9–C8



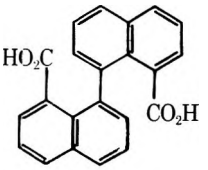
angle of the naphthalene nucleus. C1–C9–C8 angle opening can be especially effective, because the distance between the peri substituents is increased without a concomitant increase in crowding between the substituent and the adjacent naphthyl proton. Out-of-plane splaying would involve displacement of the peri substituents (and to a lesser extent, the naphthalene atoms C1 and C8) to opposite sides of the naphthalene plane.

Recent x-ray investigations[19] demonstrate a surprising lack of rigidity of the naphthalene ring and show that nonbonded interactions between bulky peri substituents are considerably relieved by large in-plane and out-of-plane distortions of the type described above. The strain energy is effectively absorbed by the naphthalene nucleus; this is accomplished by a distribution of the strain throughout the framework which includes angle bending, bond stretching and compression, and in- and out-of-plane nuclear displacements. Distortions are substantial.[20–22] In 1,8-diphenylnaphthalene[3,22] the C1–C9–C8 angle is forced open to over 126°, the C9–C1-phenyl angles open to more than 125°, and the naphthyl–phenyl out-of-plane angles are about 2°. Such distortions can become even larger. For example, in the related *peri*-diphenylacenaphthene, due to a pinching effect at the 4,5 carbon atoms, the C1–C9–C8 angle is 129.4°.[23] For the extremely crowded 1,8-diiodonaphthalene, the C1–C9–C8 angle exceeds 130°.[24]

These x-ray determined structures provide insight into the geometry of the rotational transition state of the 1,8-diarylnaphthalenes, although to achieve the more highly strained geometry of the rotational intermediate, the distortions must be considerably enhanced. Because of the considerable flexibility of the naphthalene nucleus, the dramatic lowering of the rotational barriers of both 1,8-diphenylnaphthalene and 1,4,5,8-tetraphenylnaphthalene as compared with [3.3]paracyclophane and [3.4]paracyclophane becomes understandable. The reason is that the cyclophanes lack the possibility of phenyl–phenyl splaying. The low barriers of peri-substituted naphthalenes compared with systems **3**, **4**, **5**, and **6** are also understandable because in peri-substituted naphthalenes the ground-state strain is sufficiently large to allow the transition state for rotation to be achieved more readily than for simple ortho-substituted biphenyl derivatives, where ground-state interactions are small.

The difference between the rotational barriers in 1,8-diphenylnaphthalene and 1,4,5,8-tetraphenylnaphthalene derivatives is also seen as a consequence of the involvement of the naphthalene ring distortions in the phenyl ring rotation. The tetraphenyl compound has crowding interactions at both pairs of peri positions, making this molecule more strained than the 1,8-diphenylnaphthalene. The increased strain enhances the distortion of the naphthalene nucleus and consequently facilitates attainment of the rotational transition-state geometry. Evidence of this synergistic distortion is shown by the ground-state geometries of these two molecules, as determined by x-ray diffraction.[22] The distribution of the distortion is somewhat different in these molecules,[22] but the tetraphenyl compound has the larger overall phenyl–phenyl splaying as shown by the ground-state dihedral angle between the two phenyl rings in 1,8-diphenylnaphthalene of 20° and that in 1,4,5,8-tetraphenylnaphthalene of about 36°.

A further example consistent with conjoint peri distortion and ring rotation is provided by the comparison of the ease of racemization of the binaphthyl derivatives, 8,8′-dicarboxy-1,1′-binaphthyl, **20**, and 2,2′-dicarboxy-1,1′-binaphthyl, **21**. A cursory inspection of the structural formulas, **20** and **21**, might lead one to expect rather similar restrictions to a 180° rotation about the naphthyl–naphthyl bond. In fact, resolved **21** shows no change in optical activity after 8 h at 175 °C,[25a] while **20** has a half-life with respect to racemization of only



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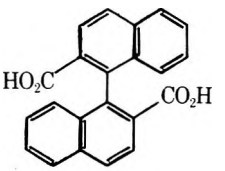

21

about 15 min at 50 °C (roughly comparable to α,α'-binaphthyl itself).[25b] However, the ground-state peri crowding in **20** is highly conducive to the naphthalene splaying interaction necessary for rotation. The low rotational barriers in other peri-substituted naphthalene derivatives, such as **9** and **10**, can be accounted for in the same way.[11]

Experimental Section

Triphenylcinnamylphosphonium Chloride, 14. Triphenylcinnamylphosphonium chloride was prepared by the method of Organic Syntheses.[26] From 40 g (0.26 mol) of (3-chloropropenyl)benzene and 92 g (0.35 mol) of triphenylphosphine was obtained 101 g (93%) of **14** (mp 224–226 °C (lit.[27] mp 224–226 °C)) which was used without further purification.

1-(3-Chlorophenyl)-4-phenyl-1,3-butadiene, 15. The procedure from Organic Syntheses[26] for 1,4-diphenyl-1,3-butadiene was slightly modified for making the chlorinated derivative. Thus, 630 mL of 0.2 M lithium ethoxide (prepared from the dissolution of 2.1 g of lithium wire in 1.5 L of absolute ethanol) was added with stirring to a solution of 50 g (0.121 mol) of **14** and 18.04 g (0.127 mol) of *m*-chlorobenzaldehyde in 150 mL of absolute ethanol. A deep red-orange color developed, which faded after the mixture had been stirred at room temperature for 45 min. Addition of 600 mL of H_2O caused formation of precipitate, which was collected and washed with 150 mL of 60% aqueous ethanol. The crude diene was stirred with a solution of ethanol (20 mL) and refiltered to give 21 g (0.087 mol, 69%) of glossy, pale-yellow plates, which melted at 109–110 °C after recrystallization from ethanol–isopropyl alcohol and from cyclohexane: NMR δ ($CDCl_3$) 6.2–7.5 (m); IR (Nujol) 1009, 1092, 770 cm^{-1}; mass spectra Calcd for $C_{16}H_{13}Cl$ 240.0706, 240.0706. Anal. Calcd for $C_{16}H_{13}Cl$: C, 79.83; H, 5.44: Cl, 14.73. Found: C, 79.60; H, 5.56; Cl, 14.46.

1,2-Dibenzoyl-3-(3-chlorophenyl)-6-phenylcyclohex-4-ene, 16. When the Diels–Alder reaction of **15** with *trans*-dibenzoylethylene was carried out in gently refluxing isopropyl alcohol for 8 h, only a brown oil resulted; however, the product could be prepared in reasonable yield under more vigorous conditions. Thus, 18 g (0.075 mol) of **15** and 20 g (0.08 mol) of *trans*-dibenzoylethylene were refluxed vigorously (no stirring; bath temperature = 136 °C) in 300 mL of isopropyl alcohol for 18 h. The mixture was allowed to cool to 50 °C and when the walls of the vessel were scratched with a glass stirring rod a white solid precipitated. The solid was removed by filtration at 50 °C, rinsed twice with 30 mL of warm isopropyl alcohol, then dissolved in acetone (1.5 mL/1 g) and filtered, and the filtrate was evaporated slowly to dryness yielding 15.5 g of **16** (0.033 mol, 44%). The infrared spectrum showed the presence of two carbonyl peaks, a major peak, at 1680 cm^{-1}, and a minor peak, at 1697 cm^{-1}, both different from the starting material peak (1600 cm^{-1}). Repeated recrystallizations failed to yield a sharply melting material. When the reaction was carried out with 24 h of reflux, the product showed almost exclusively the 1680-cm^{-1} peak. Recrystallization from isopropyl alcohol–acetone gave a white, crystalline solid (mp 136.5–139.5 °C); mass spectra Calcd for $C_{32}H_{25}ClO_2$ 476.1542, 476.1543. Aromatization of either the product with the two carbonyl peaks (presumably a mixture of isomers) or that with the single peak, by the method described below, gave similar good yields of compounds having identical spectra.

1,2-Dibenzoyl-3-(3-chlorophenyl)-6-phenylbenzene, 17. To a solution of 20.3 g (0.043 mol) of **16** in 130 mL of chloroform stirred under reflux was added dropwise (15 min) a solution of 90 mL of chloroform containing 4.3 mL of bromine. As the refluxing continued, large amounts of HBr were evolved. When the gas evolution had ceased (~30 min), the solvent was removed with a rotary evaporator to give a yellow-brown gummy substance which was crystallized by stirring overnight with absolute ethanol. Further purification was effected by stirring the finely powdered solid with 20 mL of methanol for 20 min and washing with 5 mL of methanol to yield 18 g (0.038 mol, 89%) of a white, crystalline solid which was recrystallized from isopropyl alcohol–acetone to give opaque rods: mp 150–153 °C; IR (Nujol) 1670 cm^{-1}; mass spectra Calcd for $C_{32}H_{21}ClO_2$, 472.1231, 472.1230.

4-(3-Chlorophenyl)-1,3,7-triphenylisobenzofuran, 13. Zinc dust (7 g), activated by stirring with dilute NaOH solution, then washed with water and ethanol, was added with stirring to a refluxing solution of 7.5 g (15.9 mmol) of **17** and 7 g of NaOH in 165 mL of ethanol. Refluxing for short reaction times was found to give only partial conversion. During 6 h of reflux, the solution turned bright yellow-green and then faded. The reaction mixture was filtered into 150 mL of glacial acetic acid, and 20 mL of water was added to the filtrate. The solution was evaporated to about 25 mL, and the heterogeneous aqueous mixture was extracted twice with benzene. The combined organic portions were filtered through 15 g of anhydrous sodium sulfate, evaporated to a syrupy yellow liquid, and left standing overnight to yield 6.5 g (14.2 mmol, 89%) of a brilliant-yellow solid having a powerful green fluorescence in benzene: mp 174.5–177 °C; IR (Nujol) 1470, 855 cm^{-1} (no carbonyl); mass spectra Calcd. for $C_{32}H_{21}ClO$ 456.1282, 456.1281. Anal. Calcd for $C_{32}H_{21}ClO$: C, 84.11; H, 4.63; Cl, 7.76. Found: C, 84.23; H, 4.92; Cl, 7.80.

Adduct of 13 with Acrolein, 18. Freshly distilled acrolein (5 mL) was added to a stirring, gently refluxing solution of 6.5 g (14.2 mmol) of **13** in 50 mL of benzene. After 30 min, an additional 2 mL of acrolein was added. Twenty minutes later, the bright yellow had faded to give a nearly colorless solution, and the reaction was stopped. The crude mixture was evaporated to dryness and crystallized from 10 mL of isopropyl alcohol to give a white product (6 g, 11.7 mmol, 83%): mp 148–151 °C; IR (Nujol) 1725 cm^{-1} (carbonyl); NMR δ ($CDCl_3$) 9.3 (m, 1), 3.4 (m, 1), 2.5 (m, 2), 6.6–6–7.6 (m, 21); mass spectra showed only peaks due to the retro-Diels–Alder product, **13**. Anal. Calcd for $C_{35}H_{25}O_2Cl$: C 81.94, H 4.91, Cl 6.91. Found: C 82.11, H 4.68, Cl 6.86.

5-(3-Chlorophenyl)-1,4,8-triphenyl-2-naphthaldehyde, 19. Anhydrous, gaseous HCl was bubbled for 25 min through a stirred solution of 7 g (13.7 mmol) of **18** in 50 mL of glacial acetic acid at 0 °C. The starting material largely dissolved, yielding a reddish solution. The reaction mixture was stirred for an additional hour without cooling after the addition of the HCl was stopped. The chilled mixture was filtered and the filtrate was rinsed with 8 mL of cold acetic acid. The crude yellow product (5 g, 10.1 mmol, 74%) was contaminated with **13**. Stirring with a small amount of isopropyl alcohol removed most of this impurity. Recrystallization from isopropyl alcohol gave light-yellow crystals of **19**: mp 208–210 °C; IR (Nujol) 1683 cm^{-1} (aromatic aldehyde); mass spectra Calcd for $C_{35}H_{23}ClO$ 494.1437, 194.1437.

1-(3-Chlorophenyl)-4,5,8-triphenylnaphthalene, 12. The attempted decarbonylation of **19** with tris(triphenylphosphine)rhodium(I) chloride in refluxing benzene resulted only in precipitation of the red dimer of the rhodium complex, a result which has been observed before with other sterically crowded aldehydes.[28] Nitriles are reported to stabilize the monomeric rhodium species.[28] When 1 g of **19** was heated at 160–165 °C in 9 mL of benzaldehyde, the reaction was judged complete by TLC analysis after 8 min. Chromatography of the crude mixture on silica gel with hexane as the eluent afforded **12** (0.80 g, 80%). Recrystallization from hexane gave clear prisms: mp 216–217 °C; NMR δ ($CDCl_3$) 7.5 (broad singlet, 4), 7.0 (broad singlet 19); mass spectra Calcd for $C_{34}H_{23}Cl$ 466.1490, 466.1488

Preparation of Carbinol 11. All equipment was dried immediately before use in an oven at 150 °C overnight. The reagents were transferred to the reaction vessel in a drybox under argon. A positive pressure of argon was maintained in the reaction vessel throughout the course of the reaction. A solution of 0.23 g (0.5 mmol) of **12** in 5 mL of ether was combined with 0.04 g of lithium dust (Alfa Chemical Co., 140 mesh) and 2 drops of bromobenzene. The solution was refluxed with stirring for 20 min; a deep purple color was observed 2 min after the start of refluxing. The mixture was added to a solution of 1 mL of anhydrous acetone in 10 mL of ether and, after 5 min, was hydrolyzed. Two successive preparative TLC runs using 15% ether in benzene (R_f 0.45) gave 0.14 g (57%) of **11** as clear oil: IR (Nujol) 3590 cm^{-1} (O–H stretch); NMR δ ($CDCl_3$) 7.46 (s, 4), 6.85–7.15 (s, 19), 1.48 (s, 6), 1.90 (broad s, 1); ^{13}C NMR (in ppm relative to Me_4Si, in $CDCl_3$) 31.4 (methyl), 81.0 (hydroxyl carbon); mass spectra Calcd for $C_{37}H_{30}O$ 490.2293, 490.22965.

Rotational Barrier Measurements. The proton spectra for the rotational-barrier measurement of **11** were obtained over a temperature range of 70 to −30 °C using a Varian Associates HR-220 NMR spectrometer. The temperature was determined for each measurement from the peak separations of standard samples of either methanol or ethylene glycol. The methyl signal from **11** broadened steadily from a sharp singlet at the high-temperature limit to the coalescence point at 5 °C. The peak separation reached a maximum of 3.6 Hz at −10 °C. The natural line width of the methyl peak was taken to vary linearly from 1.1 to 1.5 Hz over the temperature range examined.

Computer-simulated line shapes were obtained with the program CLATUX[29] and were visually matched to the experimental spectra. From the pre-exchange lifetimes, the free energy of rotation was calculated for each measurement using the equation $\Delta G^{\ddagger} = 4.575T(10.32 + \log T - \log K_r)$. Good agreement was obtained, particularly for measurements made in the coalescence region. From the values between −11 and +38 °C, a $\Delta G^{\ddagger}$ of 14.9 ± 0.2 kcal/mol was obtained.

Registry No.—**11**, 64682-91-3; **12**, 64728-28-5; **13**, 64682-94-6; **14**, 1530-35-4; **15**, 27331-30-2; **16**, 64754-24-1; **17**, 64728-29-6; **18**, 64682-93-5; **19**, 64682-92-4; *m*-chlorobenzaldehyde, 587-04-2; *trans*-dibenzoylethylene, 959-28-4.

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(16) In the absence of phenyl ring rotation, derivatives of 1,4,5,8-tetraphenylnaphthalene having a substituent in the meta position of one phenyl ring must exist as enantiomers. Whether or not ring rotation is rapid in solution, the possibility existed that the enantiomers could crystallize separately, as has been observed for other large dissymmetric aromatics including heptahelicene. Microscopic examination of crystals of **12** grown by slow evaporation of a hexane solution revealed that they are triclinic but have a center of symmetry and belong to the pinacoidal class, indicating that **12** crystallizes as a racemic mixture.
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(18) One recent result (R. L. Clough and J. D. Roberts, *J. Am. Chem. Soc.*, **98**, 1018 (1976)), readily understood with the model of phenyl ring rotation through an intermediate having this geometry, is the rotational barrier of 1,8-di-*o*-tolylnaphthalene which is 8 kcal/mol higher than that measured for **2**. The magnitude of the barrier is such that the postulated stable cis and trans isomers are capable of isolation. The increased barrier with 1,8-di-*o*-tolylnaphthalene is the result of unfavorable interactions of the *o*-methyl groups with the naphthyl C2 hydrogen atom in the rotational transition state.
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Centrosymmetric 1,5-Naphthyridine Derivatives: Synthesis, Tautomerism, and Thermal Rearrangements[1]

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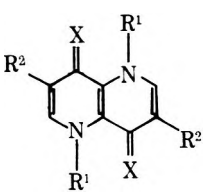
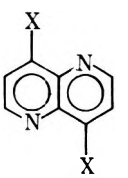
Efficient syntheses of the centrosymmetric 1,5-napthyridine derivatives **2**–**8** are reported. The 8-methoxy-1,5-naphthyridine **14** has been shown to undergo thermal rearrangement to its *N*-methyl isomer and thermal disproportionation to *N*,*N*-dimethyl and normethyl compounds. Tautomerism in hydroxy-1,5-naphthyridines has been investigated by UV spectroscopy in aqueous solution. Under these conditions the compounds studied exist predominantly as the pyridone tautomers. A remarkable alkylation reaction of the naphthyridine ring has been observed in the course of Lander rearrangement of **8**. It has been found that **8** via its rearranged isomer **4** gives the centrosymmetric ring-methylated compound **5** when heated in the solid state with methyl iodide.

Introduction

In connection with our studies of organometallic coordination polymers that might prove useful as semiconductors,[3] we needed heteroaromatic compounds potentially capable of functioning as tetradentate ligands. We were particularly interested in obtaining tetradentate analogues of the well-known bidentate chelating agent 8-hydroxyquinoline (**1**). Such analogues could be derived on paper by incorporating two additional coordination sites across a center of symmetry in **1** or by substituting naphthyridine to form appropriate 4,8-disubstituted 1,5-naphthyridines. In the present work, we describe efficient syntheses of the centrosymmetric 1,5-naphthyridine derivatives **2**–**8**. Hydroxynaphthyridines throughout this work are shown schematically and named as their presumably more stable pyridone (i.e., keto) tautomers, and evidence is presented that the latter tautomers indeed predominate in aqueous solution. Finally, we report novel results obtained during thermal rearrangement studies on alkoxynaphthyridines.



2, X = O; R¹ = R² = H
3, X = S; R¹ = R² = H
4, X = O; R¹ = Me; R² = H
5, X = O; R¹ = H; R² = Me



6, X = Cl
7, X = NH_2
8, X = OMe

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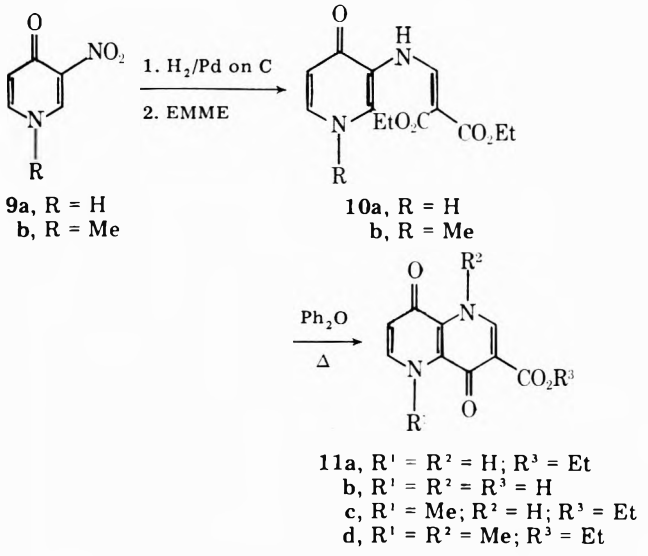
Scheme I

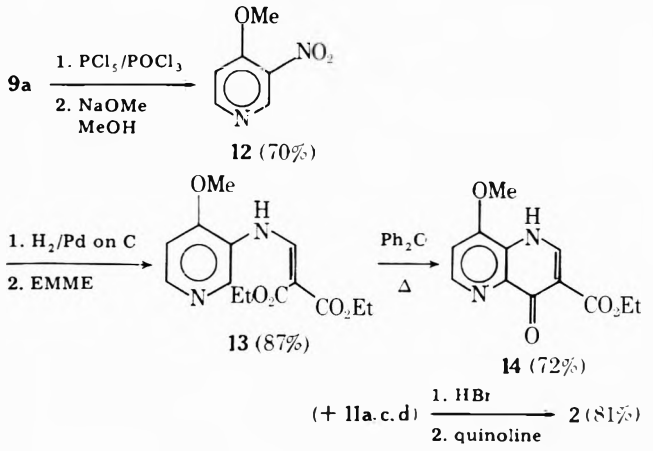


9a, R = H
b, R = Me

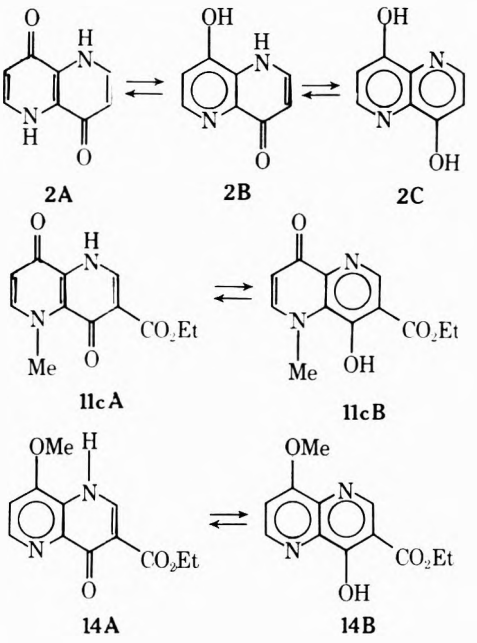
10a, R = H
b, R = Me

11a, R¹ = R² = H; R³ = Et
b, R¹ = R² = R³ = H
c, R¹ = Me; R² = H; R³ = Et
d, R¹ = R² = Me; R³ = Et

Scheme II



Scheme III



Results and Discussion

Our initial goal was a high-yield synthesis of 1,5-naphthyridine-4(1*H*),8(5*H*)-dione (**2**). Compound **2** had been prepared previously by Brown and Plasz[4] in an overall yield of 1% using the classical ethoxymethylene malonic ester (EMME) method (Scheme I). In this route, 3-nitro-γ-pyridone (**9a**) was catalytically reduced to the amine which was then condensed with EMME to give the adduct **10a** (58%). Thermal cyclization of **10a** gave the naphthyridine **11a** in 50% crude yield but only 4% final yield after purification. Compound **2** was obtained by basic hydrolysis of pure ester **11a** followed by thermal decarboxylation (sublimation) of acid **11b**. Repeating this work, we were not able to improve the procedure by direct hydrolysis of the crude ester **11a** under basic conditions. However, a dramatic increase in the overall yield of **2** resulted when crude **11a** was hydrolyzed in refluxing HCl. The product from the latter reaction, apparently a mixture of **11b** and **2**, was refluxed with quinoline to give **2** in 31% overall yield from **9a**.

We have also synthesized **2** by the somewhat longer route shown in Scheme II. **9a** was converted into 4-methoxy-3-nitropyridine (**12**) which was reduced to the amine and condensed with EMME to yield the adduct **13**. Cyclization to the naphthyridine **14** was accomplished by adding **13** in one portion to refluxing diphenyl ether or Dowtherm A. Reaction of **14** with refluxing HBr gave an excellent yield of the acid **11b** which readily decarboxylated to **2** in refluxing quinoline. The overall yield of **2** from **9a** in this case was consistently 35–45%.

The crucial step in the latter synthesis was the thermal cyclization of **13** to **14**. Yields of **14** were found to depend critically upon the duration of reaction, the isolated yields at various times being 6 (3 min), 38 (17 min), and 65–75% (25 min). Reaction times significantly longer than 25 min led to decreased yields of **14** because of further conversions leading to two other products.

The first of these products, isolated in small amounts even after 25–30 min, was the thermodynamically more stable *N*-methyl isomer **11c**, identified by comparison with material synthesized independently according to Scheme I (**9b** → **10b** → **11c**). Thermal rearrangements of the type **14** → **11c** have ample precedent in the pyridine[5] and quinoline[6] series, although few examples have been reported for naphthyridines.[7] Studies on methoxypyridines[8] have shown the rearrangement to be an intermolecular process. **11c** could arise by intermolecular reaction involving either **13** or **14**, although **14** has to be the primary source since after 25 min most of the **13** has been consumed.

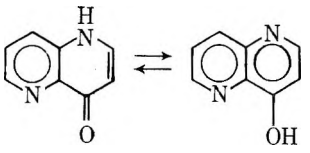
In addition to this rearrangement, we found that as the concentration of **11c** in the reaction mixture increased a disproportionation involving **14** and **11c** became important. Thus, when **13** was refluxed with diphenyl ether for 2 h, a refractory mixture containing **14**, **11c**, and the disproportionation products **11a** and **11d** resulted.[9] Refluxing **14** itself with diphenyl ether for 6.5 h produced qualitatively similar results, except that only traces of **14** remained, a fact facilitating separation of the other compounds. In this case, the *N*,*N*-dimethylnaphthyridone **11d** could be isolated by selective recrystallization followed by gradient sublimation.

The fact that analytically pure **14** did not exhibit a sharp melting point suggests that the aforementioned rearrangement and disproportionation occur more rapidly in the solid state, as might be expected in view of their intermolecular nature. Both **14** and its 8-ethoxy analogue[10] began melting at about 215 °C and were still partially solid at 270 °C.

Reaction of **2** with $POCl_3$ in a sealed tube yielded the known[4] 4,8-dichloro-1,5-naphthyridine **6** (75–82%). Treatment of **6** with ammonia in refluxing phenol gave 4,8-diamino-1,5-naphthyridine **7** (50–60%). Finally, 1,5-naphthyridine-4(1*H*),8(5*H*)-dithione **3** was obtained in essentially quantitative yield by treating **6** with hydrogen sulfide in refluxing aqueous ethanolic potassium hydroxide. Dithione **3** was stable in the solid state for at least six months but autoxidized slowly in dilute solution (see Experimental Section).

The poor solubility of **3** in the usual solvents precluded determination of its NMR spectrum.

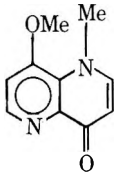
Tautomerism Studies. The γ-hydroxynaphthyridines **2**, **11c**, and **14** are capable of pyridone–pyridinol type tautomerism as depicted in Scheme III. It is well known[11] that, except in certain special cases, pyridone-type tautomers predominate in polar solvents and in the solid phase. The few studies which have been carried out on tautomerism in hydroxynaphthyridines[12] have led to similar conclusions. In particular, it has been shown[12a] by UV spectroscopy that 1,5-naphthyridin-4(1*H*)-one (**15A**) is the major tautomer in polar solvents, while the pyridinol tautomer **15B** predominates in nonpolar ones.



15A **15B**

We have studied tautomerism in the compounds in Scheme III by UV spectroscopy in aqueous solution only. Their UV spectra were compared among themselves and with the spectra of model compounds containing *N*- or *O*-methyl groups. Two appropriate models for compound **2** were 4,8-dimethoxy-1,5-naphthyridine (**8**) and 1,5-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione (**4**). The *O,O*-dimethyl compound **8** was easily synthesized by reaction of **6** with sodium methoxide in methanol. As expected, **8** rearranged readily on heating to the isomer *N,N*-dimethyl derivative **4** (vide infra). The structures of **8** and **4** were established by standard spectroscopic methods and single crystal x-ray analysis.[13]

UV spectral data for all relevant compounds are summarized in Table I. The spectrum of the *N,N*-dimethyl derivative **4** closely resembles that of **2**. Both possess a strong absorption maximum at 232 nm and two further maxima between 315 and 350 nm. Also, both spectra bear a formal resemblance to that of the known pyridone tautomer **15A**, which has a strong maximum at 240 mm and a single maximum at 323 nm. In contrast, the UV spectrum of the *O,O*-dimethyl derivative **8** does not resemble that of **2** but instead is quite similar to the spectrum of pyridinol tautomer **15B**. Both **8** and **15B** absorb strongly around 225 nm and less intensely at about 284 nm.



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These observations clearly eliminate the dipyridinol tautomer **2C** and suggest that the dipyridone tautomer **2A** predominates in aqueous solution. The data, however, do not rigorously exclude the pyridinol–pyridone tautomer **2B**. Despite several attempts, we were not able to synthesize the model corresponding to **2B**, namely, the *N,O*-dimethyl derivative **16**. Nevertheless, if **2B** were the major tautomer in solution, then a priori one would expect the spectrum of **2** to show the characteristic absorption maxima present in the spectra of both **4** and **8**. In other words **2** should exhibit a band in the region 250–300 nm corresponding to the long-wavelength band in the spectrum of **8**. This is exactly what happens in the case of **14**, a compound which has one ring only frozen in the pyridinol form. Here there are three bands, at 245, 304, and 317 nm, expected for a compound with a pyridinol–pyridone structure. Consequently, if **14** exists predominantly as the pyridone tautomer **14A**, then the absence of a prominent band around 250–300 nm in the spectrum of **2** is evidence that **2B** is not the principal tautomer in solution. A similar argument can be applied in the case of **11c**. Its spectrum resembles those of **2** and its dipyridone model **4**, in possessing only two prominent long-wavelength bands, both above 300 nm. The spectrum of **11c** is, moreover, virtually identical with that of the dipyridone **11d**, the only model for **11c** available. It therefore seems clear that the predominant tautomer of **11c** in aqueous solution is **11cA**.

Table I. UV Spectral Data for 1,5-Naphthyridine Derivatives

Compd	Registry no.	γ_{max}, nm	ε
15A[a]		240	27 200
		323	10 600
15B[b]		230	36 100
		286	5 940
2	64761-13-3	232	38 500
		262	3 200
		318	19 600
		330	27 400
4	63086-89-5	232	30 700
		267	3 000
		335	19 600
		348	21 300
8	63086-86-2	222	51 400
		282	10 000
11c	64761-17-7	232	29 200
		263	3 800
		319	19 400
		332	19 600
11d	64761-18-8	232	36 100
		265	4 500
		319	22 800
		333	23 000
14	64761-20-2	221	24 300
		245	16 800
		304	15 200
		317	13 600

[a] In H_2O; ref 12a. [b] In dioxane; ref 12a.

Thermal Reactions of 8 and Synthesis of 5. We have studied thermal reactions of the *O,O*-dimethyl compound **8** under a variety of conditions in sealed ampules. When **8** was heated in the solid state for 10 h at 226 °C, the *N,N*-dimethyl isomer **4** was isolated in 62% yield. As expected, the solid-state reaction could be catalyzed by methyl iodide (Lander rearrangement[14]). Heating **8** with 1 molar equiv of methyl iodide (2.5 h/226 °C) gave **4** in 78% isolated yield. Catalysis by methyl iodide even allowed the reaction to be carried out in solution. Thus, when **8** was heated in diphenyl ether with methyl iodide (0.3 molar equiv/20 min/210 °C), **4** was obtained in essentially quantitative yield. In the absence of methyl iodide, no **4** was detected after 2.5 h at 232 °C.

When **8** was heated in the solid state with methyl iodide (0.3 molar equiv/220 °C) for 12 h instead of 2.5 h, a new compound **5** was obtained (53%) which had properties similar to those of **2**. Specifically, **5** sublimed only above 230 °C and possessed at least one acidic hydrogen, the material being soluble in base and reprecipitated with acid. The IR spectrum of **5** resembled closely that of **2** in the region above 1500 cm^{-1}. The UV spectrum of **5** in water suggested that it was a dipyridone, the principal absorption bands appearing at 240 and 343 nm. Elemental analysis showed **5** to be an isomer of **8** and by a process of elimination we concluded that it had to be a ring-methylated derivative of **2**. This was confirmed by its NMR spectrum which showed two singlets at δ 2.61 (6 H) and 8.70 (2 H). Consequently we assigned **5** the centrosymmetric structure 3,7-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione.

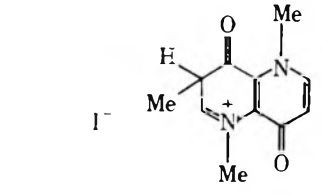
Table II. Mass Spectral Data for the Crude Product from the Reaction of 4 with Methyl-d_3 Iodide

m/e	Rel intensity
190	85
193	100
196	35
204	53
207	82
210	53
218	12
221	24
224	24

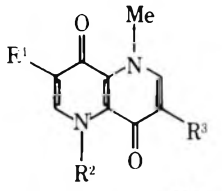
We preferred this structure to the isomeric 2,6-dimethyl derivative because the signals for two ring protons (δ 8.70) resembled those for $H_{2,6}$ (δ 8.65) in the spectrum of **2** (see end of Experimental Section).

The transformation 8 → **5** must take place via **4**, because **4** was isolated in good yield from reactions using shorter reaction times. Furthermore, **4** itself gave **5** in comparable yield when heated in the solid state with methyl iodide. In contrast, no reaction occurred when **4** was heated either in the solid state without methyl iodide or with methyl iodide in diphenyl ether solution (10 h/225 °C).

It is possible that the reaction **4** → **5** involves an electrophilic substitution, attack by methyl iodide leading to the naphthyridinium intermediate **17** which then undergoes loss of a proton and cleavage of the *N*-methyl group by iodide. This mechanism implies the formation of intermediates such as **18a–d.** A compound to which we have assigned the structure



17



18a, R^1 = Me; R^2 = R^3 = H
b, R^1 = R^2 = Me; R^3 = H
c, R^1 = R^3 = Me; R^2 = H
d, R^1 = R^2 = R^3 = Me

18a was indeed isolated in erratic amounts, and apparently contaminated with **4**, when 8 was heated with methyl iodide at temperatures somewhat below 225 °C. As the material was not isolated analytically pure, its identification must remain tentative.[15] More importantly, we have clearly detected tri- and tetramethylated species (presumably **18b–d**) in the mass spectrum of crude **5.** For example, Table II shows mass spectral data for the crude product obtained by heating **4** with methyl-d_3 iodide (0.9 molar equiv/15 h/228 °C). The *m/e* 190–196 series of peaks is due primarily to **5,** the 204–210 series to the trimethylated species, and the 218–224 series to the tetramethylated species. The absence of prominent peaks attributable to d_9 or d_{12} species indicates that no compound contains more than two CD_3 groups and that exchange of the *N*-methyl groups is not significant. The presence of d_0 tri- and tetramethylated compounds is evidence that unlabeled methyl iodide is produced in the course of the reaction. Purification of this crude mixture gave material containing <5% trimethylated compounds and no **18d** as shown by mass spectroscopy. The NMR spectrum showed the expected singlets at δ 2.61 and 8.70 in the peak area ratio of 3.3:2 in good agreement with the expectation based on the mass spectrum.

There appears to be no precedent for carbon alkylation either in the Lander rearrangement[14] or in the closely related Hilbert–Johnson reaction.[16] The apparent regiospecificity of the reaction **4** → **5** seems to rule out an alkylation mechanism involving radical intermediates, although this type of evidence is not entirely conclusive.[17]

Electrophilic alkylations of azaaromatic compounds are extremely rare.[19] An interesting example in the pyridine series is the thermal reaction of trityl chloride with 2-pyridone or *N*-methyl-2-pyridone to yield, in both cases, 5-triphenylmethyl-2-pyridone.[20] In view of this, we examined the thermal reaction of **2** itself with methyl iodide (4.5 molar equiv/12 h/228 °C). The crude product contained only traces of mono-, di-, and trimethylated species as shown by mass spectroscopy. This failure is somewhat curious, given the pyridone result. More work will be needed to resolve this anomaly.

Experimental Section

Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. IR spectra were taken on KBr pellets on a Beckman IR8 spectrophotometer. NMR spectra were determined on either a Varian A-60 or a Perkin-Elmer R-12 spectrometer. Absorptions are reported relative to an internal tetramethylsilane standard. Ultraviolet and visible spectra were obtained on a Beckman DK-2A spectrophotometer. Solutions of the rather insoluble compounds **2, 3, 5,** and **11d** were prepared for UV determination by warming a weighed amount of compound in the appropriate solvent in a volumetric flask until solution was complete. The solution was then allowed to cool to room temperature and made to volume. All UV/visible extinction coefficients were corrected for extraneous absorption determined by running the solvent in both cells. Low-resolution mass spectra were obtained on a Model 21-491 and high-resolution spectra on a Model 21-110 DuPont-Consolidated Electrodynamics Corp. instrument. Gradient sublimations were run at 0.1-mm pressure in 9-mm glass tubes heated in a cylindrical oven[21] constructed by Mr. F. C. Maseles. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Concentrated hydrobromic acid was distilled from stannous chloride dihydrate immediately before use. Predried quinoline was vacuum distilled (20 mm) from zinc dust and stored over potassium hydroxide pellets.

3-Nitro-γ-pyridone (9a). γ-Pyridone was nitrated by the method of Crowe,[22] except that the product was isolated in 55–65% yield in two crops: the first by filtration of the original acidic reaction mixture which had been poured onto ice and the second by filtration of the cold neutralized reaction mixture. Recrystallization from water and drying in a desiccator (P_2O_5) gave yellow microcrystals, mp 275–277 °C (lit.[22] 279 °C).

3-Nitro-4-chloropyridinium Hydrochloride. 3-Nitro-4-chloropyridine was prepared from **9a** by the method of Bishop et al.[23] The hydrochloride was prepared by bubbling hydrogen chloride gas through a stirred cooled ether solution of the chloro compound. The resulting moisture-sensitive precipitate was quickly filtered and stored in a desiccator in vacuo. Yields were 70–82%.

3-Nitro-4-methoxypyridine (12). The synthesis was a modification of a procedure of Bijlsma and den Hertog.[24] To an ice-cooled solution of sodium metal (5.42 g; 0.236 mol) in dry methanol (200 mL) was added dropwise with stirring a solution of 3-nitro-4-chloropyridinium hydrochloride (22.9 g; 0.117 mol) in dry methanol (200 mL) over a 1-h period. At the end of the addition, the ice bath was removed and the mixture was stirred an additional 1 h. Carbon dioxide gas was bubbled through the liquid for 20 min and then the mixture was filtered. The sodium chloride precipitate was washed several times with dry methanol and then discarded. The yellow-tan filtrate was evaporated to dryness and the residue was boiled with ether and filtered to remove a small amount of residual sodium chloride. The ether filtrate was boiled down to a convenient volume and Skelly B was added to the hot solution until turbidity was evident. Refrigeration of the solution followed by filtration gave **12** as yellow microcrystals (13 g). Two further crops were obtained from the filtrate. Final yield was 16.5 g (91%), mp 73–75 °C (lit.[25] 75 °C).

Diethyl [(4-Methoxy-3-pyridyl)amino]methylenemalonate (13). A mixture of **12** (5 g; 0.0325 mol), 10% palladium on carbon (500 mg), and dry methanol (125 mL) was hydrogenated for 6 h in a Parr apparatus at 50 psi. Filtration of the mixture through Celite and evaporation of the filtrate yielded the crude amine as a light tan oil or solid. The amine was stirred and refluxed in toluene (100 mL) with ethoxymethylenemalonic ester (EMME; 7 g; 0.0325 mol) for 24 h and then the reaction mixture was evaporated to dryness. The residue was dissolved in boiling Skelly B, filtered by gravity, and cooled to room temperature. **13** crystallized as fine, white platelets (8.8 g; 87% based

on 12), mp 98.5–100 °C, after drying in vacuo. A small amount of this material was dissolved in boiling Skelly B and filtered hot through a thin pad of Norit A on Celite. Cooling the filtrate yielded an analytical sample of **13**: mp 100–101 °C; mass spectrum *m/e* 294.1215 (M^+, calcd for $C_{14}H_{18}N_2O_5$, 294.1216); NMR ($CDCl_3$) δ 1.34, 1.39 (6 H, overlapping triplets, ethyl CH_3), 4.03 (3 H, s, OCH_3), 4.29, 4.36 (4 H, overlapping quartets, ethyl CH_2), 6.95 (1 H, d, J = 5.8 Hz, H_5), 8.34 (1 H, d, J = 5.8 Hz, H_6), 8.53 (1 H, s, H_2), 8.60 (1, H, d, J = 14 Hz, collapses to singlet on shaking with D_2O, vinyl CH), 11.00 (1 M, d, J = 14 Hz, vanishes on shaking with D_2O, NH).

Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.25; H, 6.30; N, 9.34.

Ethyl 8-Methoxy-1,5-naphthyridin-4(1*H*)-one-3-carboxylate (14). Diphenyl ether (200 mL) was heated to reflux in a three-necked flask fitted with an air condenser and a mechanical stirrer. **13** (4.5 g; 0.0153 mol) was added to the flask in one portion and the solution was refluxed and stirred for exactly 25 min. The dark-brown solution was cooled rapidly to room temperature with an air gun and poured into Skelly B (200 mL). The resulting precipitate was collected on a fritted glass funnel, washed well with Skelly B, and then boiled for several hours with benzene to remove residual diphenyl ether and again filtered through a fritted glass funnel. Addition of Skelly B to the benzene filtrate yielded variable amounts of the *N*-methyl isomer **11c** (vide infra). The precipitate on the fritted funnel was dried in a vacuum oven at 80 °C to yield crude **14** 2.72 g; 72%) as a tan powder. A small portion was twice dissolved in boiling nitromethane, filtered hot through a thin pad of Norit A on Celite, and cooled to produce analytically pure **14** as white microcrystals which partially melted beginning at about 215 °C (see Discussion): mass spectrum *m/e* 248.0795 (M^+, calcd for $C_{12}H_{12}N_2O_4$, 248.0797); NMR (F_3AcOH) δ 1.53 (3 H, t, ethyl CH_3), 4.60, 4.68 (5 H, singlet and quartet overlapping, respectively, OCH_3 and ethyl CH_2), 7.94 (1 H, d, J = 7 Hz, H_7), 9.16 (1 H, d, J = 7 Hz, H_6), 9.39 (1 H, s, H_2).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87. Found: C, 57.79; H, 4.99.

1,5-Naphthyridine-4(1*H*),8(5*H*)-dione (2). A solution of 2.74 g (0.011 mol) of **14** in 210 mL of concentrated hydrobromic acid was stirred and refluxed for 24 h. The resulting dark tan solution was evaporated to dryness on a rotary evaporator and the residue recrystallized from a large volume of water. Tan crystals of the acid **11b** were collected by filtration and dried in a vacuum oven at 100 °C. Crude yield was 1.98 g (88%): NMR (F_3AcOH) δ 7.92 (1 H, d, J = 6.5 Hz, H_7), 8.99 (1 H, d, J = 6.5 Hz, H_6), 9.48 (1 H, s, H_2).

The acid **11b** was ground to a powder and added to quinoline (90 mL), and the heterogeneous mixture was stirred and refluxed for 10 h. After cooling to room temperature, the precipitate was collected on a fritted glass funnel, washed well with acetone, and dried in vacuo. The dried precipitate was dissolved in dilute aqueous sodium hydroxide on a steam bath to give a tan solution which was filtered hot through a thin pad of Norit A on Celite. The cooled filtrate was taken to pH 6 with 2 N hydrochloric acid and the resulting precipitate was collected on a fritted glass funnel. Acidification of the filtrate to pH 2 gave a mixture of **2**, and **11b** which could be recycled in subsequent decarboxylation reactions. The precipitate on the fritted funnel was redissolved in dilute aqueous sodium hydroxide on a steam bath and then acidified to pH 2 with 2 N hydrochloric acid. The resulting precipitate was collected on a fritted glass funnel, washed well with water, and dried in a vacuum oven at 100 °C to yield **2** as a white powder (1.38 g; 88%). Recrystallization from water (3 mL/mg) gave white microcrystals: mp >300 °C (sublimes) (lit.[4] >300 °C); NMR (F_3AcOH) δ 7.53 (2 H, d, J = 7 Hz, $H_{3,7}$), 8.65 (2 H, d, J = 7 Hz, $H_{2,6}$).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 57.35; H, 3.55; N, 17.03.

2 was prepared from **11a** essentially as described above except that hydrochloric acid was substituted for hydrobromic acid in the initial hydrolysis step.

Diethyl [(1-Methyl-4-oxo-1,4-dihydro-3-pyridyl)amino]methylenemalonate (10b). The compound was prepared from *N*-methyl-3-nitro-γ-pyridone **9b**[26] by the same procedure used to make **13** from **12**. Crude **10b** was crystallized by adding Skelly B to a solution in hot benzene and cooling to room temperature. Yields were ca. 60% tan crystals, mp 131–132 °C; the material was used without further purification: NMR ($CDCl_3$) δ 1.30, 1.37 (5 H, overlapping triplets, ethyl CH_3), 3.83 (3 H, s, NCH_3), 4.25, 4.34 (4 H, overlapping quartets, ethyl CH_2), 6.43 (1 H, d, $J_{5,6}$ = 7.2 Hz, H_5), 7.38 (1 H, doublet of doublets,[27] $J_{5,6}$ = 7.2 Hz, $J_{2,6}$ = 2 Hz, H_6), 7.59 (1 H, d, J = 2 Hz, H_2), 8.39 (1 H, d, J = 14.5 Hz, collapses to singlet on shaking with D_2O, vinyl CH), 10.89 (1 H, d, J = 14.5 Hz, vanishes on shaking with D_2O, NH).

Ethyl 5-Methyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione-3-carboxyate (11c). Starting with **10b** the procedure was the same as that used to prepare **14** from **13**, except that the cyclization was performed in Dowtherm A and the reaction mixture was refluxed for only 15 min. Crude **11c** was obtained as a tan powder (mp 250–253 °C) in ca. 35% yield. An analytical sample was prepared by the method used for **14**, yielding white microcrystals: mp 262–264 °C; NMR (F_3AcOH) δ 1.58 (3 H, t, ethyl CH_3), 4.69, 4.81 (5 H, singlet and quartet overlapping, respectively, NCH_3 and ethyl CH_2), 7.42 (1 H, d, J = 7.5 Hz, H_7), 8.55 (1 H, d, J = 7.5 Hz, H_6), 9.50 (1 H, s, H_2).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.86; H, 4.80; N, 11.24.

Ethyl 1,5-Dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione-3-carboxylate (11d). Compound **14** (400 mg) was added to refluxing diphenyl ether (10 mL) and the solution was stirred and heated for 6.5 h. The reaction was worked up with Skelly B in the usual manner and the resulting precipitate was boiled with benzene. Filtration of the hot benzene mixture gave 97 mg of precipitate A, shown by IR to be a mixture of **11a** and **11d**. The yellow benzene filtrate was filtered hot through Norit A on Celite, evaporated to 15 mL, and refrigerated to yield 82 mg of precipitate B, shown by IR to be a mixture of **11c** and **11d**. Precipitate A was recrystallized from nitromethane (Norit A on Celite) to give crude **11d** (23 mg) as yellow microcrystals, mp 274–281 °C. Gradient sublimation at 200 °C yielded an analytical sample as white microcrystals, mp 282–283.5 °C; NMR (F_3AcOH) δ 1.55 (3 H, t, ethyl CH_3), 4.45–4.95 (8 H, multiplet dominated by broad singlet at 4.80, NCH_3 and ethyl CH_2), 7153 (1 H, d, J = 7 Hz, H_7), 8.57 (1 H, d, J = 7 Hz, H_6), 9.17 (1 H, s, H_2).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H. 5.39. Found: C, 59.24; H, 5.36.

4,8-Dichloro-1,5-naphthyridine (6). To a heavy-walled glass tube (28-cm long; 2-cm o.d.) was added **2** (335 mg; 0.0021 mol) and phosphorus oxychloride (20 mL). The tube was sealed and immersed to a depth of 4 cm in an oil bath at 175–185 °C. Solid **2** dissolved in about 6 h to yield a green solution. The tube was cooled and opened, and the solution was rinsed out with a little $POCl_3$ and evaporated on a rotary evaporator. The green viscous residue was carefully decomposed with ice and then neutralized with 2 N aqueous ammonia. The resulting gray precipitate was collected and dried in a vacuum desiccator (P_2O_5). The dried precipitate was dissolved in benzene, filtered hot through a thin pad of Norit A on Celite, and evaporated down to a convenient volume. Skelly B was added to the hot solution until turbidity was evident, and the solution was allowed to cool slowly to room temperature and was finally cooled in an ice bath. **6** crystallized as white needles (340 mg; 82%), mp (sealed tube) 274–276 °C (lit.[4] 278–279 °C).

4,8-Diamino-1,5-naphthyridine (7). The procedure was a modification of that described by Case and Brennan[28] for 4-amino-1,5-naphthyridine. To a 50-mL, three-necked flask fitted with an efficient condenser, a thermometer, and a fritted glass gas inlet tube was added warm phenol (20 mL). Ammonia gas passed through a potassium hydroxide drying tower was bubbled into the phenol for 10 min after which **6** (601 mg; 0.003 mol) was added to the flask and the solution was heated to 170–180 °C while the gas flow continued. Periodically, the white precipitate which formed on the gas inlet tube was scraped back into the reaction mixture. After 10 h, the tan solution was cooled, basified with 25% aqueous sodium hydroxide, and poured into a 125-mL flask. Addition of water to the dark-green solution at this point occasionally caused the product to precipitate but the following procedure was more reproducible. Additional 10% aqueous sodium hydroxide was added to the solution to make a final volume of about 75 mL. The flask was placed in a refrigerator for 18 h and the resulting white precipitate was collected and washed twice with ice water. The dried precipitate was dissolved in warm 2 N sulfuric acid, filtered, cooled, and adjusted to pH 8 with saturated aqueous sodium carbonate solution. Care must be taken around pH 5–6, since the mixture then becomes colloidal and froths. The precipitate was collected, washed with ice water, and dried to give **7** as white microcrystals (272 mg; 56%), mp 252–255 °C (dec). An analytical sample, prepared by recrystallization from water, had mp 255–257 °C (dec); NMR (4:1 Me_2SO-d_6/$CDCl_3$) δ 6.58, 6.68 (6 H, singlet and doublet partially overlapping, respectively, $J_{2,3}$ = 5.5 Hz, NH_2 and $H_{3,7}$), 8.22 (2 H, d, $J_{2,3}$ = 5.5 Hz, $H_{2,6}$); UV γ_{max} (H_2O) 235 (ε 37 000), 328 nm (13 600).

Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.73; H, 5.20; N, 34.72.

1,5-Naphthyridine-4(1*H*),8(5*H*)-dithione (3). To a 50-mL, three-necked flask fitted with an efficient condenser and a fritted glass gas inlet tube was added a solution of potassium hydroxide (5.5 g) in ethanol/water (9:1; 35 mL). Hydrogen sulfide gas was passed through the solution for 2 h and then the gas flow was shut off while **6** (1 g;

0.005 mol) was added to the flask. The gas flow was shut off while **6** (1 g; 0.005 mol) was added to the flask. The gas flow was resumed and the mixture was gently refluxed. White crystalline **6** gradually dissolved and the mixture turned deep orange. Periodically, the orange precipitate which formed on the gas inlet tube was scraped off into the reaction mixture. After 12 h, the orange solution was washed into a 125-mL flask with water and any orange precipitate was dissolved by adding a few pellets of solid potassium hydroxide. The solution was filtered and then carbon dioxide gas was passed through the liquid for 20 min. Dark orange crystals of **3** were collected on a fritted glass funnel, washed with water, and dried in a desiccator (P_2O_5). The yellow filtrate, containing traces of **3**, turned colorless in about 25 h as the dithione autoxidized. The dried product weighed 940 mg (96.4%): mp >300 °C; UV γ_{max} (CH_3CN) 246 (sh, ϵ 14 900), 260 (19 400), 328 (6000), 410 (sh, 7400), 450 nm (13 400). Within 30 h the yellowish-orange acetonitrile solution became colorless and exhibited the following UV/visible spectrum: 222 (ϵ 15 900), 238 (sh, 13 500), 263 (sh, 8300), 318 (9200), 330 (10 500). The latter extinction coefficients were calculated on the assumption that the molecular weight of the autoxidized compound remained 194.

Anal. Calcd for $C_8H_6N_2S_2$: C, 49.46; H, 3.11; N, 14.42; S, 33.01. Found: C, 49.54; H, 3.07; N, 14.45; S, 32.82.

4,8-Dimethoxy-1,5-naphthyridine (8). To a magnetically stirred solution of 210 mg (9.13 mmol) of sodium metal in 75 mL of dry methanol was added 834 mg (4.19 mmol) of **6** and the mixture was heated to reflux. Within 2 h 6 had all dissolved and the reaction was thereafter monitored by TLC (silica gel/$CHCl_3$). Refluxing was continued for either 96 h or until the TLC spot corresponding to the monomethoxy- monochloronaphthyridine intermediate had vanished. The solution was cooled and carbon dioxide gas was passed through the liquid for 15 min. The solution was evaporated to dryness and the residue dried in a vacuum desiccator (P_2O_5). The dried residue was boiled three times with 75-mL portions of acetone, the undissolved solid being collected on a fritted glass funnel between each step. The combined acetone filtrates were evaporated to dryness and the residue was dissolved in boiling benzene. Skelly B was added to the boiling solution until turbidity was evident and the solution was allowed to cool slowly to room temperature and was finally cooled in an ice bath. The resulting white crystals were collected and vacuum dried to give 692 mg (87%) of **8**, mp 209–212 °C. An analytical sample prepared by gradient sublimation at 95 °C melted at 214–216 °C. Crystals grown by this method were large enough for x-ray structure determination: NMR (F_3AcOH) δ 4.64 (6 H, s, OCH_3), 8.03 (2 H, d, J = 6.5 Hz, $H_{3,7}$), 9.36 (2 H, d, J = 6.5 Hz, $H_{2,6}$).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.97; H, 5.47; N, 14.49.

General Procedures for Thermal Reactions of 4 and 8. All solid-state reactions were carried out in sealed ampules totally immersed in a wax bath. For solid-state reactions employing methyl iodide, the reactants were usually blanketed with a small amount of mineral oil to facilitate sealing the ampule. The reactions were worked up by washing the ampule contents onto a fritted glass funnel with Skelly B. Reactions in diphenyl ether were run in sealed ampules immersed in a wax bath to the level of the liquid in the ampules. The latter reactions were worked up by pouring the ampule contents into Skelly B and filtering.

Thermal Reactions of 8. A. Solid State. Compound **8** (280 mg) was heated at 226 °C for 10 h. The crude product was dissolved in boiling benzene and filtered hot through a thin pad of Norit A on Celite. Cooling the filtrate yielded white crystalline **4** (174 mg; 62%), mp 268.5–272 °C. An analytical sample prepared by gradient sublimation at 110 °C melted at 273–275.5 °C: NMR ($CDCl_3$) δ 4.30 (6 H, s, NCH_3), 6.43 (2 H, d, J = 8 Hz, $H_{3,7}$), 7.37 (2 H, d, J = 8 Hz, $H_{2,6}$); NMR (F_3AcOH) δ 4.79 (s, NCH_3). (The solution was not concentrated enough to distinguish any other peaks. Upon standing, there formed in the solution crystals of the bis(trifluoroacetate salt) of **4** large enough for x-ray analysis.)

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.97; H, 5.40; N, 14.62.

B. Solid State with Methyl Iodide. **8** (140 mg) was heated with methyl iodide (34 mg; molar ratio = 1:0.33) at 220 °C for 12 h. The crude product was boiled with benzene to remove any **4** present and then gradient sublimed at 275 °C. The white crystalline sublimate was dissolved in warm dilute aqueous sodium hydroxide and the resulting violet solution was acidified to pH 2 with concentrated hydrochloric acid. The precipitate was collected and recrystallized from a large volume of water to yield analytically pure **5** (74 mg; 53%): mp >300 °C; NMR (F_3AcOH) δ 2.61 (6 H, s, CH_3), 8.70 (2 H, s, $H_{2,6}$); UV γ_{max} (H_2O) 233 (sh, δ 37 400), 237 (sh, 45 700), 240 (51 600), 273 (4300), 332 (sh, 17 400), 337 (sh, 18 300), 343 nm (23 300).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.98; H, 5.40; N, 14.67.

Heating **8** with methyl iodide at temperatures below 225 °C for 12 h produced complex mixtures of products from which an impure compound identified as **18a** could be isolated in erratic yields by gradient sublimation at 132–150 °C. The material was contaminated with **4** and exhibited: mp 228–235 °C; NMR (F_3AcOH) δ 2.57 (s), 4.79 (s), 7.47–7.87 (m), 8.47–8.95 (m), peak area ratios 7:10:3:5.5, respectively; UV γ_{max} (H_2O) 232 (ϵ 33 600), 267 (3500), 297 (sh, 5000), 325 (20 000), 338 nm (24 800).

Heating **8** (40 mg) with methyl iodide (34 mg; molar ratio 1:1.14) for 2.5 h at 200–220 °C produced **4** (31 mg) which was isolated by gradient sublimation at 132 °C and identified by mp, IR, and UV.

C. Solution. Heating **8** (50 mg) in diphenyl ether (1 mL) for 2.5 h at 232 °C yielded 45 mg of recovered **8** identified by IR.

D. Solution with Methyl Iodide. Heating **8** (45 mg) in diphenyl ether with methyl iodide (9 mg; molar ratio 1:0.27) for 23 min at 210–213 °C yielded 44 mg of **4** which was identified by IR.

Thermal Reactions of 4. A. Solid State. Heating **4** (22 mg) for 10 h at 225 °C yielded 22 mg recovered **4** which was identified by IR.

B. Solid State with Methyl Iodide. **4** (63 mg) was heated with methyl iodide (57 mg; molar ratio 1:1.20) for 17 h at 220–226 °C. The crude product was boiled with benzene and dried to yield 41 mg of material with the IR identical to that of **5**. The mass spectrum showed traces of tri- and tetramethylated derivatives in addition.

When **4** (52 mg) was heated with methyl-d_3 iodide (34 mg; molar ratio 1:0.86) for 16 h at 228 °C, the crude product showed the mass spectrum given in Table II. Purification of the material by dissolution in dilute aqueous sodium hydroxide and reprecipitation with acid yielded material with the following properties: mass spectrum m/e (relative intensity) 190 (95), 193 (100), 196 (32), 204 (4), 207 (9), 210 (3); NMR (F_3AcOH) δ 2.61 (s), 8.70 (s), peak area ratios 3.3:2, respectively.

C. Solution with Methyl Iodide. Heating **4** (32 mg) with methyl iodide (7 mg; molar ratio 1:0.28) in diphenyl ether for 10 h at 225 °C yielded unchanged **4** (29 mg) which was identified by IR.

Attempted Reaction of 2 with Methyl Iodide. Heating **2** (46 mg) with methyl iodide (182 mg; molar ratio 1:4.5) for 12 h at 228 °C gave 47 mg of material which was identified as unchanged **2** by IR. The mass spectrum of the product showed traces of mono-, di-, and trimethylated species in addition.

Assignment of ^{1}H NMR Spectra. All the naphthyridine derivatives with four unsubstituted positions (2,3,6,7) showed two signals for the corresponding CH protons, separated by 1.3–1.5 ppm. These were assigned by analogy with 4-pyridone, where the signals for the protons adjacent to nitrogen appear downfield by 1.3 ppm relative to those adjacent to carbonyl (δ 7.92, 6.62, respectively[29]).

Registry No.—**3**, 64761-22-4; **5**, 63086-87-3; **6**, 28252-80-4; **7**, 64761-26-8; **9b**, 64761-30-4; **10b**, 64761-14-4; **11a**, 64761-28-0; **11b**, 64761-15-5; **12**, 31872-62-5; **13**, 64761-16-6; **18a**, 63086-88-4; 4-methoxy-3-pyridinamine, 33631-09-3; ethyl ethoxymethylenemalonate, 87-13-8; 3-nitro-4-chloropyridinium hydrochloride, 54079-68-4; methyl iodide, 74-88-4.

Supplementary Material Available. Table III, IR spectral data, and Table IV, mass spectral data, for 1,5-naphthyridine derivatives and precursors, (7 pages). Ordering information is given on any current masthead page.

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New Aspects of Intramolecular Hydrogen Transfer in Some Ortho-Substituted Aryl Radicals

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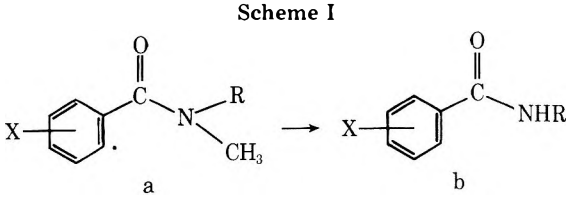
Intramolecular 1,5-, 1,6-, and 1,7-hydrogen transfers are observed when *o*-di-*n*-propylaminosulfonylbenzenediazonium tetrafluoroborate (**1a**) is decomposed in the system: $CuBr_2$–Me_2SO. The reaction competes with the "Sandmeyer-like" aryl bromide formation. The extent of competition is shown, by study of lower homologues, to reflect steric effects which are also evident from a comparison of the similar dediazoniation of *o*-di-*n*-propylamino- and *o*-dimethylaminocarbonylbenzenediazonium ions, **8a** and **8c**, respectively. The stereochemical argument is amplified by the failure of *o*-*n*- and -isopropoxycarbonylbenzenediazonium salts to undergo hydrogen transfer. A large solvent effect is also evident; the substitution of acetone for Me_2SO in decomposition of **8c** decreases hydrogen transfer from near 90 to about 15%, with a corresponding increase in bromoarene formation. The ultimate products of hydrogen transfer are identified and rationalized.

The demethylation of *o*-(dimethylaminocarbonyl)aryl or (*N*-aryl-*N*-methylaminocarbonyl)aryl diazonium salts by intramolecular 1,5-hydrogen transfer in homolytic fashion (Scheme I) was probably first recognized in 1954.[1] Despite extensive study of its mechanism,[2] there are still many unanswered questions which merit further work.[2b,c] It is, however, already apparent that the manner and the medium in which the radical a (Scheme I) is generated play an important role in product determination,[3a] and that when R is a substituted aryl, steric influences have been recognized.[1,3b,c]

In connection with a synthetic project, we happened upon a related reaction which also involved radical transfer, but to a propyl group of a dipropyl sulfonamide (Figure 1). Astonishingly, attack occurred at the α, β, and γ positions! The 6-, 7-, and 8-membered cyclic transition states that were required for this reactivity suggested that there were steric and other influences not previously recognized in this type of process. We have, accordingly, briefly examined some of them. Our experimental method comprised adding a dimethylsulfoxide (Me_2SO) solution of the *o*-diazonium tetrafluoroborates to $CuBr_2$ in Me_2SO, a system which is reported to give bromoaromatics in high yield,[4,5] our original goal. The use of $CuBr_2$–Me_2SO ensured a homolytic reaction, and the high concentration could also be expected to minimize rearrangement of the alkyl radicals[6] prior to oxidation and termination in products. Since this system had not previously been used to generate the analogous carboxamide radicals, we examined two of these, and, for reasons which will become clear, we also studied the behavior of two esters.

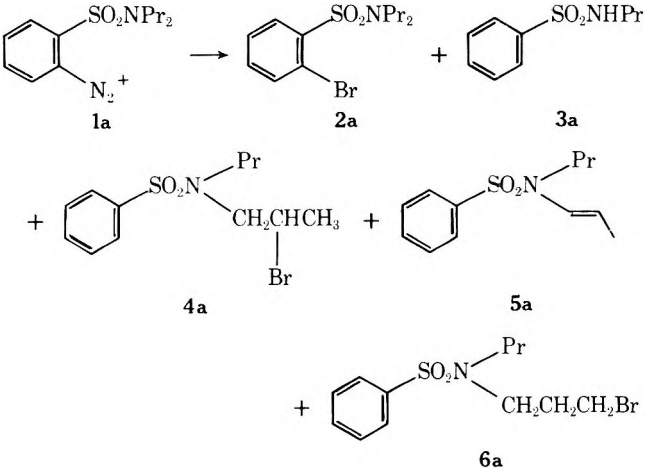
Scheme I



Results

The instantaneous decomposition of o-(dialkylaminosulfonyl)benzenediazonium tetrafluoroborates **1** in $CuBr_2$–dry Me_2SO at room temperature furnished *o*-bromobenzenesulfonamides **2** from a Sandmeyer-like[7a] reaction, along with products resulting from transfer of the initially generated aryl radical site to the alkyl side chain.[7b] These latter products included monoalkyl sulfonamides, bromoalkyl sulfonamides, and alkenylalkyl sulfonamides (Scheme II), reflecting hy-

Scheme II



0022-3263/78/1943-1337$01.00/0

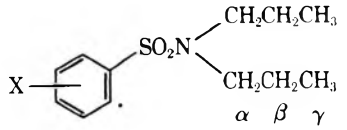


Figure 1.

Table I. Yield of Products (%)[a] from the Decomposition of 1 in $CuBr_2$–Me_2SO

Product	1a, R = n-C_3H_7	1b, R = C_2H_5	1c, R = CH_3
o-$BrC_6H_4SO_2NR_2$ (2)	32	43	75
$C_6H_5SO_2NHR$ (3) (α-abstraction)	20	24	<2
$C_6H_5SO_2NRR'$ (4) (β-bromo)	32	10	
$C_6H_5SO_2NRR''$ (5) (enamide)	6	3	
$C_6H_5SO_2NRR'''$ (6) (γ-bromo)	7		
$C_6H_5SO_2NR_2$ (7) (reduction)	2	4	4

[a] **4a**, R′ = $CH_2CHBrCH_3$; **4b**, R′ = CH_2CH_2Br; **5a**, R″ = $CH{=}CHCH_3$; **5b**, R″ = $CH{=}CH_2$; **6a**, R‴ = $CH_2CH_2CH_2Br$. A small amount (1.5%) of $C_6H_5SO_2N(C_2H_5)CH{=}CHBr$ (**5d**) was also isolated from the reaction of **1b**. Approximately 10–12% of "dimeric" ether **3d** was formed from **1c** (see text for discussion). The yields reported were determined by preparative SiO_2 chromatography or GLC determination against standards.

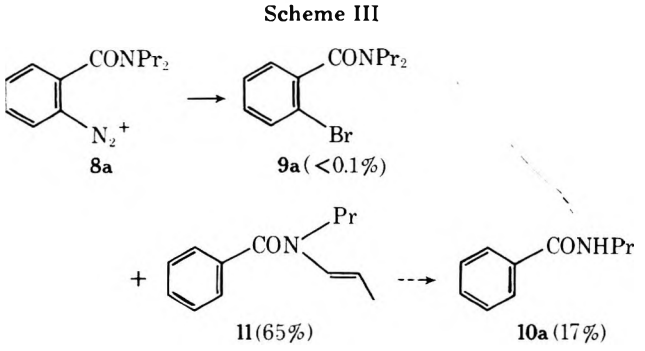
drogen abstraction from each of the aliphatic carbon atoms. A small amount of reduction product, dialkyl benzenesulfonamide **7**, was invariably reduced by what must be an intermolecular reaction. The yields of general products are summarized in Table I. Ethers were formed from two molecules, particularly in the case of **1c**, by what was probably an ionic process. Their characterization was incomplete, but nevertheless secure.

The effect of moisture on the reaction was assessed in the case of **1b**, the diethyl homologue. Both *N*-(β-bromovinyl)-*N*-ethylbenzenesulfonamide (**5d**) and *N*-ethyl-*N*-vinylbenzenesulfonamide (**5b**), minor products which formed in dry solvent, were not detected using Me_2SO containing 0.1% moisture. An experiment employing reverse addition of the reactants showed that higher bromide concentrations favored Sandmeyer product formation over hydrogen transfer.

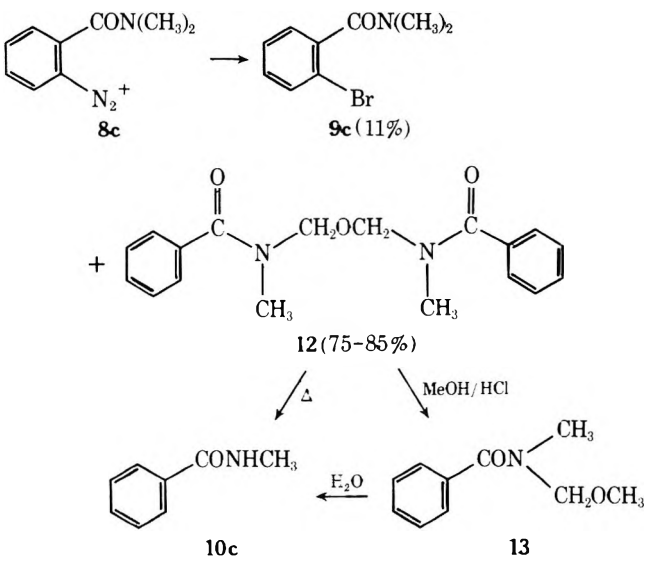
No Sandmeyer product **9a** was detected from decomposition of the dipropyl carboxamide **8a**, (Scheme III), nor was there any evidence for 1,7-hydrogen transfer. The products which were seen were (mono) *N*-propylbenzamide (**10a**) and the enamide **11**, products of 1,5- and 1,6-hydrogen transfers, respectively.

Dimethyl carboxamide **8c** gave, in $CuBr_2$–Me_2SO, only 11% bromide **9c** and ca. 75–85% of 2,6-dibenzoyl-2,6-diaza-4-oxaheptane (**12**), which although not obtained in pure form

Scheme III

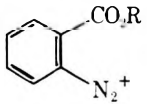


Scheme IV



was thoroughly and unambiguously identified (Scheme IV). A small and variable amount (2–10%) of *N*-methylbenzamide (**10c**) was detected by GLC. In contrast, decomposition of **8c** in $CuBr_2$–acetone gave 78% of Sandmeyer product and 14% of **10c**.

The diazonium salts **14a** and **14b**, prepared from *n*- and



14a, R = n-C_3H_7
b, R = i-C_3H_7

isopropylanthranilate, respectively, gave high yields of Sandmeyer product without any evidence for radical transfer products. The ubiquitous reduction products were observed here just as they were with the sulfonamides and carboxamides.

Discussion

As stated in the introductory section, 1,5-intramolecular hydrogen abstractions have previously been observed with some o-carboxamide radicals. The formation of **4**, **5**, and **6** (Table I) constitutes, to the best of our knowledge, the first authentic examples of 1,6- and 1,7-hydrogen abstractions by an aryl radical.[8]

Some of the studies by Cohen et al., utilizing isotopically labeled **8c** showed that the radical transfer step was exceedingly rapid[9] in terms of conformational motion of some of the involved atoms, and we have no reason not to extrapolate their conclusions, at least qualitatively, to our system. This being so, one can make a case that the ratios of α-, β-, and γ-abstraction products obtained from **1a** represent, roughly, the conformational preferences of **1a**. Conformational preferences were previously invoked in explaining the anomalously low reactivity in some intermolecular hydrogen transfers to aryl and other radicals.[10] The rate at which hydrogen atoms are transferred to such a hot aryl radical site[9] largely precludes attainment of conformational equilibrium during the fleeting existence of the radical per se.

Sulfonamides. It is clear from the yields shown in Table I that the hydrogen transfer products dominate the reaction of **1a** and that the Sandmeyer bromoarene **2c** prevails with the much less encumbered dimethyl homologue. The diethyl case, starting with **1b**, occupies an intermediate position. The yield of bromide **2b** from it, 43%, may be compared with the sum of **2a** (32%) and **6a** (7%), the latter coming from a γ-car-

Table II. Effect of Reaction Conditions on the Decomposition of 1b

Product	Conditions[a,b] A	B	C
2b	54.8	62.8	34.2
3b	26.8	27.8	32.0
4b	12.2	9.3	16.9
5b	4.8	0	14.8
5d	1.5	0	2.2

[a] Standard conditions described in the Experimental Section (A); used undried Me_2SO (B); inverse addition of reactants (C). [b] Values are given in GLC area (%).

bon transfer process not available to **1b**. On the other hand, when considering the minimally crowded dimethyl homologue **1c**, even the α-carbon hydrogen transfer diminishes in importance compared to the Sandmeyer path, accentuating a picture of steric obstruction to the approach of Br^- with **1a** and **1b**. A preparatively useful yield (60%) of analytically pure **2c** may, in fact, be obtained by one crystallization of its total reaction mixture.

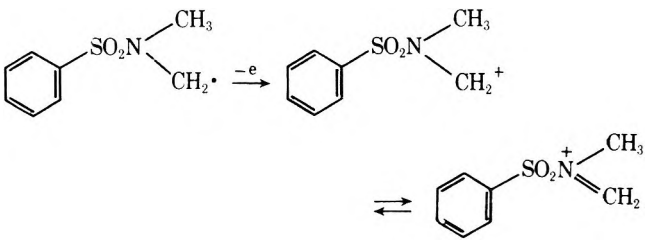
Hydrogen transfer in the case of **1c** gave not the simple demethylation product **3c**, but $C_6H_4SO_2N(CH_3)$-$CH_2OCH_2N(CH_3)O_2SC_6H_5$ (**3d**) which was readily converted to **3c** during chromatography. Its formation may be rationalized in the same way as **12**, an entirely analogous product from the corresponding carboxamide, which is discussed below in the section in carboxamides.

It is quite reasonable that both fundamental reaction routes (i.e., leading to Sandmeyer or hydrogen transfer products) compete from the same initial aryl radical and not from some other unidentified reactive species. Support for this view comes from an experiment in which the product ratio was altered by reversing the order of reactant addition. In that case, $CuBr_2$–Me_2SO solution was added slowly to **1b** in Me_2SO, limiting the concentration of Br^- in the system. The yield of bromoarene **2b** dropped from 43 to 27%, while the yields of **3b**, **4b**, and **5b** increased accordingly, as measured by GLC area ratios (Table II). The increase in **5b** was the greatest of the three, further suggesting a role for Br^- concentration in determining the product split from the β-alkyl radical. We believe that enamides **5a** and **5b** arise from a β-carbon radical by oxidative elimination either with or without the intermediacy of an organocopper species,[6,11] although their formation from an α-carbon radical similarly cannot be strictly ruled out by our data. The ease with which the latter should and does suffer either dealkylation or ether formation (see below) with the dimethyl homologue, and even more evidently with the carboxamide **8c**, suggests these latter processes are the most important outlets for α-carbon radicals. Their resonance-enhanced stability resulting from the adjacent nitrogen[10] would also favor continued oxidation by the reagent to α-carbenium ions like that postulated in anodic oxidations of dimethyl benzamide,[12] as suggested in Scheme V.

Dehydrobromination of bromoalkylamides **4a** and **4b** to the enamides **5a** and **5b** is unlikely in view of the demonstrated stability of the former to GLC and silica gel chromatography. Vinyl derivative **5b**, however, is susceptible to hydrolysis, and is not recovered from silica gel chromatography in benzene–methanol. Moreover, it is not even detected when the dediazoniation of **1b** is performed in Me_2SO containing as little as 0.1% water (Table II).

Bromovinyl sulfonamide **5d** is an unusual product, owing its identification to the power of modern spectroscopic tools. Its obviously arises from a double oxidation. We did not find double oxidation products from other substrates, and we offer

Scheme V



no insight into its formation. It was only a minor product, ca. 1.5%; however, its formation was reproducible.

In summary, the major features of the reactions of sulfonamides **1a–c** can be related to previous studies of **8c** in different media, but modified by sensible steric arguments.

How does **8c** itself behave in the same medium, and what are the differences which are introduced in a larger homologue?

Carboxamides. We expected and found steric influences based on the differing bond lengths and angles of the >C=O vs. $>SO_2$ bridging groups. The absence of radical attack upon the γ-methyl group of the dipropyl carboxamide **8a** (cf. 7% with **1a**) and the lack of Sandmeyer product from the same substrate (cf. 32% with **1a**, 11% with **8c**) are clear examples (Scheme III). Polar effect differences of the aryl radical[13] cannot be responsible for the latter; the two-carbon insulator eliminates any explanation based upon differences in nitrogen basicity[10] in the former.[14] Despite the fact that 1,5-hydrogen abstractions are generally favored over 1,6 abstractions on steric grounds, **8a** shows a reversal in preference of ca. 4:1. This reversal in preference strengthens the case for conformational control in this fast reaction.

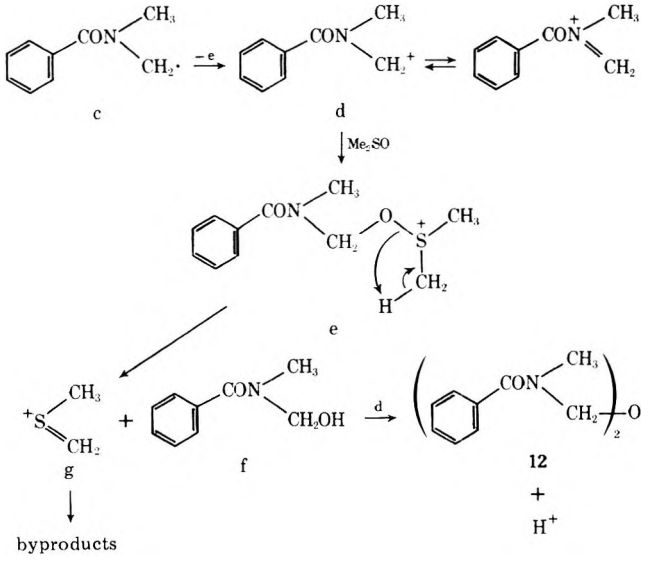
Incidentially, if we reject the hypothesis that the enamides result from β-carbon attack, and are another product of initial α-carbon attack, then we would have, in the case of **8a**, a *regiospecific* reaction at the α-carbon site. This seems very unlikely in view of the many observations reported above.

Other aspects of the carboxamide reactions deserve mention. We suggest that the total lack of a β-bromoalkyl product analogous to **4a** reflects greater electron density at the nitrogen atom which can stabilize transition to an enamide more readily than can the nitrogen in sulfonamide **1a**.

The 11% yield of Sandmeyer product **9c** in Me_2SO contrasts with the decomposition of the same substrate in chloride-containing aqueous media.[2a] In that case, 44.6% of *o*-(*N*,*N*-dimethyl)chlorobenzamide was formed. We suspect that the solvent plays a more important role than the different nucleophile, especially since decomposition of **8c** in acetone–$CuBr_2$ yields 77.5% of **9c**. Zollinger's group, in studying the effect of solvents on dediazoniation, invoked charge transfer complex formation with Me_2SO in a pre-rate-determining step of the decomposition of the *p*-nitrobenzenediazonium ion.[15] On the other hand, Sandmeyer reaction in Me_2SO to form aryl chlorides is inferior to the similar aryl bromide synthesis.[4]

Formation of the "dimeric" product (**12**, Scheme IV) from decomposition of **8c** merits comments, too. Initial examination of the reaction by GLC showed a small amount of **9c** and **10c** as the only volatile compounds, contrasting with TLC evidence of a major product different from those two. Preparative chromatography was accompanied by decomposition, as were initial attempts at mass spectroscopy. NMR spectra of the total reaction mixture suggested that this major product contained singlet aromatic, methyl, and methylene protons in integrated ratios of 5:3:2.[16a] The aliphatic groupings were broad, but they sharpened on heating,[16b] suggesting the well-known phenomenon attributed to restricted rotation of an *N*,*N*-dialkyl amide. Decomposition of **12** became evident at 80 °C, and after carrying it to its completion the resulting

Scheme VI



product could be clearly identified at **10c**. Particularly diagnostic for such a dealkylation process is the appearance of the lower field ortho aromatic protons, signifying allowed coplanarity of the ring and carbonyl moieties.

At the same time, solvolysis of a sample in methanol–HCl was followed by GC–MS, and formation of **10c** was shown to arise through the intermediacy of **13**. Structure **12** was thus supported by this chemistry and the ^1H and ^{13}C NMR chemical shifts for its methylene group. Further reinforcement then came from mass spectroscopy (chemical ionization); a strong M + 1 ion (*m/e* 313) was formed with isobutane as the reactant gas. Indeed, even a mass spectrum (field desorption) was eventually obtained showing M^+ 312. As noted above, structures similar to **12** have been formed by anodic oxidation of *N,N*-dialkyl amides.[12]

The involvement of Me_2SO in homolytic dediazoniation has recently been demonstrated by the inclusion of an ^{18}O label from the solvent into the product.[15] A similar occurrence could explain the presence of the ether oxygen in **12**, although an ionic pathway may be more likely in view of the enhanced stability of a carbenium ion intermediate. We have adapted the ideas of Ross[12] and Zollinger[15] in describing a plausible sequence to **12** (Scheme VI). The attack of Me_2SO on carbenium ion d to give e may be followed by bond reorganization as pictured, or stepwise, to give alcohol f and the methylenesulfonium ion g. The former, alcohol f, could be expected to yield **12** in reaction with another ion d upon loss of a proton.

Modest amounts of such an ether **3d** arose also from **1c**, as indicated by ^{13}C NMR spectra and solvolytic enhancement of the yield of **3c**. Formation of its higher homolgue from **1b** could also be supported from the ^{13}C NMR spectra of the total reaction.

Our last argument for steric effects rests on the failure of the ester analogues **14a** and **14b** to yield radical transfer products. No electronic reasons preclude hydrogen abstraction from the side chain; in fact, an adjacent oxygen increases reactivity at C_α, compared to a hydrocarbon, albeit not as much as does an adjacent nitrogen.[10] Beyond the α position, all electronic distinctions between the esters and amides should vanish. Even though rotation may occur freely in the alkoxycarbonyl moiety, we suggest that because of the diazo function, there is little concentration, if any, of a conformer having alkyl hydrogens near the proradical site. In the rapid reaction which occurs, hydrogen transfer cannot compete with attack by bromide.

Experimental Section[17]

Starting materials were made from the corresponding *o*-nitro acid chlorides followed by catalytic reduction over PtO_2 in alcohol. The only aniline not previously reported was ***N,N*-di-*n*-propyl-2-aminobenzenesulfonamide**, bp 148–150 °C (0.1 mm). Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93. Found: C, 56.22; H, 7.76; N, 10.76.

Me_2SO (J. T. Baker) was dried over molecular sieves before use, except as noted. All other reagents and solvents were reagent grade and were used as received.

Diazonium salts were made according to the general procedure reported here for **1a**. A solution of 5.3 g (20.7 mmol) of *N,N*-di-*n*-propyl-2-aminobenzenesulfonamide in 10 mL of isopropyl alcohol and 4 mL of 48% HBF_4 (28 mmol) was cooled and stirred at 0–5 °C while adding 3.1 mL (23 mmol) of isoamyl nitrite. When crystallization was essentially complete, generally 10–40 min, 100 mL of ether was added, and the crystalline salt was collected and washed with ether. After drying in vacuo at ~23 °C, the salt weighed 6.9 g (19.4 mmol, 94%).

All yields were uniformly high. The ^1H NMR spectra (Me_2SO-d_6) were as expected; decomposition in the solvent *without* catalyst was shown to occur, but at an inconsequential rate compared to the catalyzed reactions (see below).

Dediazoniations were performed according to the general procedure, except as noted, reported here for **1b**. A solution of 190 mg (0.58 mmol) of **1b** in 0.5 mL of Me_2SO was added dropwise with stirring to 2.5 mL of Me_2SO containing 420 mg of $CuBr_2$ at 17–23 °C. Gas evolution was apparent and instantaneous. After 8–10 min, the mixture was diluted with methylene chloride, poured into ice and water, and worked up in the usual way.

Products. In each case the crude product mixture from a decomposition was studied by NMR spectroscopy, GLC, TLC, and sometimes GC–MS. Most yields reported in the text, tables, and Experimental Section were obtained either from silica gel chromatography on preparative plates or from GLC. They are accurate to ca. 3%. Some (e.g., the ethers) are obviously approximations. The individual sections below describe in brief the examination of each product mixture and the characterization for each product which was identified.

Dipropyl Sulfonamide 1a. Preparative plate chromatography (95:5 hexane–ethyl acetate) of 205 mg of mixture gave four bands, which are described in order of increasing polarity.

Band A: 10.2 mg of **5a**; mass spectrum, *m/e* 239 (M^+, 25), 210 (30), 198 (15), 141 (75), 77 (85), 70 (100); the ^1H NMR ($CDCl_3$) spectrum showed vinylic protons at δ 4.9 (m) and 6.5 (d).

Band B: 142 mg; contained nearly equal amounts of **2a** and **4a** and ~3% of **7a**. Rechromatography (benzene) allowed separation of the major constituents. **2a:** mass spectrum, *m/e* 321 (M^+), 319 (4), 292, 290 (100), 250, 248 (13), 221, 219 (63), 157, 155 (78). **4a:** mass spectrum, *m/e* 321 (M^+), 319 (0.4), 292, 290 (4), 240 (3), 212 (100), 170 (15), 141 (58), 77 (69); the ^1H NMR ($CDCl_3$) spectrum showed a methyl doublet at δ 1.75 and a methine multiplet at δ 4.35; the ^{13}C NMR ($CDCl_3$) spectrum showed the methine carbon at δ_c 46.75.

The small amount of **7a** was identified by GC comparison (mixed injection) with an authentic sample; GC–MS, *m/e* 241 (M^+).

Band C: 16.5 mg of **6a**; mass spectrum, *m/e* 321 (M^+), 319 (3), 292, 290 (55), 212 (82), 141 (100), 77 (64); the ^1H NMR ($CDCl_3$) spectrum showed a triplet at δ 3.40 for $-CH_2Br$; the ^{13}C NMR spectrum ($CDCl_3$) showed this carbon at δ_c 30.42.

Band D: 26.8 mg of **3a**; identified by GC comparison (mixed injection) with an authentic sample. Mass spectrum, *m/e* 199 (M^+, 5), 170 (53), 141(59), 77 (100).

Diethyl Sulfonamide 1b. Preparative plate chromatography (99:1 benzene–methanol) of 154 mg gave the following in order of increasing polarity.

Band A: 2.9 mg (~1.5%) of *N*-(β-bromovinyl)-*N*-ethylbenzenesulfonamide (**5d**); mass spectrum, *m/e* 291 (M^+, 10), 289 (M^+, 8), 146 [$M^+ - (Br + SO_2)$, 48], 141 (23), 125 (52), 77 (100). 69 (32).

Band B: 11.3 mg, which upon reexamination by GLC was a gross mixture containing all the known products as well as some which were not identified.

Band C: 92.6 mg (52%); contained **2b** and **4b** in ca. 4.5:1 ratio, respectively. Rechromatography gave substantially pure samples of each. **2b:** mass spectrum, *m/e* 293 (M^+), 291 (10), 278 (100), 276 (97), 221 (58), 219 (56), 157 (52), 155 (53); the ^1H NMR ($CDCl_3$) spectrum showed the aromatic, methylene and methyl protons in the ratio 4:4:6. **4b:** mass spectrum, *m/e* 293 (M^-, 5), 292 (3), 291 (M^+, 5), 290 (2), 278 (16), 276 (18), 228 (16), 212 (4), 198 (100), 141 (65), 77 (98); in the ^1H NMR ($CDCl_3$) spectrum the $BrCH_2CH_2-$ signal was found as a single line at δ 3.45.

Band D: 5.2 mg, most of which was nonvolatile. A small amount of **7b** was identified by GLC comparison with an authentic sample.

Band E: 24.8 mg (24%) of *N*-ethylbenzenesulfonamide (**3b**); identified by comparison with an authentic sample.

The enamide **5b** was clearly identified by GC–MS and ^{13}C NMR spectra of the original crude mixture (mass spectrum, *m/e* 211 (M^+, 0.2), 185 (9), 170 (31), 141 (46), 77 (100), 51 (off scale); the ^{13}C NMR spectrum showed the terminal methylene at δ_c 92.6), but it was not found after silica gel chromatography. Its yield (3%) was estimated from GLC area (%) only.

When the same reaction was repeated identically, except that undried Me_2SO was used (H_2O, 1.13 mg/mL by Fisher titration), the unsaturated compounds **5b** and **5d** were undetectable (see Table II). The inverse addition reaction, performed by slowly adding 2.5 mL of dry Me_2SO saturated with $CuBr_2$ to 190 mg of **1b** in 1 mL of dry Me_2SO, gave the full spectrum of products, but in different proportions (Table II).

Dimethyl Sulfonamide 1c. An aliquot of a preparative scale reaction mixture was crystallized from methanol to give **2c**, mp 59–61 °C, in 60% direct yield; mass spectrum, *m/e* 265 (M^+), 263 (42), 221 (18), 219 (14), 184 (13), 157 (53), 155 (55), 44 (100); ^1H NMR ($CDCl_3$) δ 2.86 (s, 6, CH_3), 7.3–8.2 (m, 4, aromatic).

Anal. Calcd for $C_8H_{10}BrNO_2S$: C, 36.37; H, 3.82; N, 5.30; Br, 30.25. Found: C, 36.71; H, 3.64; N, 5.31; Br, 30.17. Chromatography of the mother liquors (9:1 benzene–methanol) gave an additional 15% of **2c**.

Another experiment was assayed by GLC using octadecane as an internal standard. It showed yields of 71, 11, and 4.5% for **2c**, **3c**, and **7c**, respectively. After warming a portion of the total reaction mixture at 60 °C in methanol and aqueous HCl for 60 h, the amount of **3c** increased. The increase was attributed to hydrolysis of $C_6H_5SO_2N(CH_3)CH_2$–O–$CH_2N(CH_3)SO_2C_6H_5$, evidence for which was a ^{13}C NMR signal at δ_c 74.3, which was a triplet according to an off-resonance decoupling experiment. The fact that **3c** was undetectable in the ^{13}C NMR spectrum of the reaction before hydrolysis suggests that its observation by GLC represents thermal decomposition on the column.

Dipropyl Carboxamide 8a. Distillation of a preparative-sized reaction mixture gave pure **11**, bp 132–134 °C (4 mm) [lit.[18] bp 155–159 °C (13 mm)]; mass spectrum, *m/e* 203 (M^+, 11), 188 (4), 105 (100), 77 (4); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3, CH_3), 1.6 (d, 3, CH_3CH=), ~1.6 (m, 2, CH_2), 3.65 (t, 2, CH_2), 5.0 (d of q, 1, $CHCH_3$), 6.5 (brd d, 1, NCH), 7.4 (brd s, 5, aromatic).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; 6.89. Found: C, 76.61; H, 8.19; N, 6.59.

Recoveries from preparative thin-layer chromatography were 65% of **11** and 17% of **10a** [mass spectrum, *m/e* 163 (M^+, 29), 105 (100), 77 (33)], which behaved identically (GLC, TLC, NMR) with an authentic sample. A trace of *N,N*-dipropylbenzamide was visible by GLC. No other products of significance were detectible by ^1H or ^{13}C NMR spectroscopy of the mixture. When the reaction was run by adding solid **8a** to the $CuBr_2$ solution, a number of other minor products were formed in addition to **10a** and **11**.

Dimethyl Carboxamide 8c. Quantitative GLC showed 2–3% of **10c** and traces of *N,N*-dimethylbenzamide, both identical with authentic samples, and an 11% yield of bromocarboxamide **9c**, identical in all respects with a sample prepared from *o*-bromobenzoyl chloride and dimethylamine: bp 144 °C (3.6 mm); mass spectrum, *m/e* 229 (M^+), 227 (23), 228, 226 (30), 185, 183 (100), 157, 155 (43), 148 (25), 76 (81), 75 (70); ^1H NMR ($CDCl_3$) δ 2.8 (s, 3, CH_3), 3.1 (s, 3, CH_3), 7.0–7.7 (m, 4, aromatic).

Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.20; H, 4.48; N, 6.03.

The ^1H NMR spectrum ($CDCl_3$) of the entire crude reaction mixture showed signals attributable to **12**: δ 2.95 (brd s, 3, CH_3), 4.65 (brd s, 2, CH_2), 7.35 (brd s, 5, aromatic); ^{13}C NMR signals for the methyl and methylene groups were broad and centered at δ_c 34 and 77, respectively; mass spectrum (chemical ionization, isobutane), *m/e* 313 ($M^+ + 1$).

A small portion of the reaction mixture containing an internal GLC standard was heated over the weekend at 60 °C in methanol containing a few drops of HCl. GLC analysis showed 85.5% of **10c** and 11% of **9c**. A sample of this hydrolysis taken after ~2 h of reaction time showed a product whose mass spectrum identified it as **13**; mass spectrum, *m/e* 179 (M^+, 12), 164 (20), 148 (4), 105 (100), 77 (35). **13** was absent at the end of the hydrolysis. Decomposition carried out in dry acetone instead of Me_2SO gave 78% of **9c** and 14% of **10c**, as measured by quantitative GLC. Bromoacetone was also formed.

Ester 14a. The product consisted of 11% *n*-propyl benzoate and 89% *n*-propyl *o*-bromobenzoate (**15a**), as measured by GLC. Authentic **15a** was prepared from the corresponding acid chloride: bp 123 °C (4 mm); mass spectrum, *m/e* 244 (M^+), 242 (7), 202, 200 (58), 185, 183 (100), 157, 155 (42), 104 (14), 76 (83), 75 (70).

Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found C, 49.46; H, 4.83.

Ester 14b. GLC measured yields of 6% isopropyl benzoate and 94% isopropyl *o*-bromobenzoate (**15b**) were obtained from reaction in the usual way. Authentic **15b** was made from the corresponding acid chloride: bp 92 °C (4 mm); mass spectrum, *m/e* 244 (M^+), 242 (21), 202, 200 (42), 185, 183 (100), 157, 155 (26), 104 (11), 76 (46), 75 (39).

Acknowledgment. It is with great pleasure that we dedicate this paper to Dr. John M. Chemerda in appreciation for his stimulating, provocative, and skillful research leadership. We also acknowledge the stimulating discussion with Professor T. Cohen of the University of Pittsburgh and Drs. A. W. Douglas and R. A. Firestone of these laboratories.

Registry No.—**1a**, 65000-08-0; **1b**, 65000-09-1; **1c**, 65000-10-4; **2a**, 65000-11-5; **2b**, 65000-12-6; **2c**, 65000-13-7; **3a**, 23705-37-5; **3c**, 5183-78-8; **3c**, 65000-14-8; **4a**, 65000-15-9; **4b**, 65000-16-0; **5a**, 65000-17-1; **5b**, 65000-18-2; **5d**, 65000-19-3; **6a**, 65000-26-2; **8a**, 65000-20-6; **8c**, 22396-44-7; **9c**, 54616-47-6; **10a**, 10546-70-0; **11**, 19326-67-1; **12**, 65000-21-7; **13**, 65000-22-8; **14a**, 65000-23-9; **14b**, 65000-24-0; **15a**, 65000-25-1; **15b**, 592-47-52-8; *N,N*-dipropyl-2-aminobenzenesulfonamide, 65000-27-3; *o*-bromobenzoyl chloride, 7154-66-7; Me_2SO, 67-68-5; $CuBr_2$, 7789-45-9.

References and Notes

(1) D. H. Hey and D. G. Turpin, *J. Chem. Soc.*, 2471–2481 (1954).
(2) For leading references, see: (a) A. H. Lewin, A. H. Dinwoodie, and T. Cohen, *Tetrahedron*, **22**, 1527–1537 (1966); (b) D. H. Hey, G. H. Jones, and M. J. Perkins, *J. Chem. Soc., Perkin Trans. 1*, 1170–1171 (1972); (c) T. Cohen, K. W. Smith, and M. D. Swerdloff, *J. Am. Chem. Soc.*, **93**, 4303–4304 (1971).
(3) (a) D. H. Hey, G. H. Jones, and M. J. Perkins, *J. Chem. Soc., Perkin Trans. 1*, 1155–1161 (1972); (b) D. M. Collington, D. H. Hey, C. W. Rees, and E. le R. Bradley (nee Wessels), *J. Chem. Soc. C*, 1021–1025 (1968); (c) the "ortho-substituent effect" was first shown to be unnecessary by the results of ref 3d; (d) D. H. Hey, C. W. Rees, and A. R. Todd, *J. Chem. Soc C*, 1518–1525 (1967).
(4) M. Kobayashi, E. Yamada, M. Matsui, and N. Kobori, *Org. Prep. Proced.*, **1**, 221–224 (1969).
(5) The value of Me_2SO as a solvent for the formation of aryl radicals from diazonium tetrafluoroborates was reported by M. Kobayaski, H. Minato, N. Koburi, and E. Yamada, *Bull. Chem. Soc. Jpn.*, **43**, 1131–1135 (1970). In the *absence* of some catalytic agents, the question of homolytic vs. heterolytic decomposition is still not completely answered; see H. Zollinger, *Acc. Chem. Res.*, **6**, 335–341 (1973), for a review and leading references.
(6) C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.*, **94**, 856–865 (1972).
(7) (a) We shall henceforth refer to this process and product without the "-like" limitation, even though the "true" Sandmeyer reaction uses Cu^I salts in aqueous media. For leading references, see "The Merck Index", 9th ed, 1976, p ONR 79. (b) Radical transfer and hydrogen transfer are synonymous in the context of this paper and will be used interchangeably.
(8) (a) A 1,6 attack may have occurred with an *N*-ethylbenzanilide;[3a,d] however, no product specifically characteristic of this process was reported. (b) Breslow and his co-workers have capitalized on steric proximity, employing hydrogen abstraction by aryl-*bound* functional groups well beyond 7-bond distances. For a leading reference, see R. Breslow, R. J. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna, and R. Kalega, *J. Am. Chem. Soc.*, **99**, 905–915 (1977).
(9) Faster than carbonyl–nitrogen bond rotation, slower than nitrogen–methyl bond rotation [T. Cohen, C. H. McMullen, and K. Smith, *J. Am. Chem. Soc.*, **90**, 6866–6867 (1968)], and faster than ring–carbonyl bond rotation (ref 2c).
(10) R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3754–3765 (1963).
(11) J. K. Kochi, *Acc. Chem. Res.*, **7**, 351–360 (1974).
(12) S. D. Ross, M. Finkelstein, and R. C. Peterson, *J. Am. Chem. Soc.*, **88**, 4657–4660 (1966).
(13) G. A. Russell, *Free Radicals*, **1**, Chapter 7 (1973).
(14) A referee has suggested that attribution of the results with **8a** to a steric effect "ignores the real possibility that α abstraction may be far more favorable in the carboxamide than in the sulfonamide due to the greater electron donation in the former," thereby effectively eliminating competitive γ abstraction in that substrate. No doubt that is a factor, but if it was a significant or controlling one we would be hard pressed to explain why no γ (or indeed, α or β) abstraction occurs in the case of the esters **14a** and **14b**. We believe that an effect which fits *all* the experimental results, i.e., the steric effect, should not be minimized. Furthermore, we have not ignored the possible role of the greater basicity of the carboxamide N in the discussion of the enamide formation (see below in text).
(15) Y. Hirose, G. H. Wahl, Jr., and H. Zinnger, *Helv. Chim. Acta*, **59**, 1427–1437 (1976).
(16) (a) The NMR spectra also showed that the amount of *N*-methylbenzamide

(10c) was at the lower end of the 2–10% range observed by GLC, suggesting that some of it was a thermal product. (t) We are indebted to Mr. R. Zerfing for this experiment.

(17) Boiling points and melting points are uncorrected. Elemental analyses were performed under the direction of J. P. Gilbert of these laboratories. ^{1}H NMR spectra were obtained with Jeol (USA) C-60 HL and Hitachi Perkin-Elmer R-24 spectrometers. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer. All chemical shifts are referred to tetramethylsilane. Mass spectra were obtained courtesy of Messrs. J. Smith and H. Flynn, and Patricia Cala, using LKB 9000, Varian MAT-371, and Finnegan 3200 spectrometers. For brevity, only parts of some spectra are reported. GLC analyses were performed on a Hewlett Packard 5830A gas chromatograph using thermal conductivity detection. Three columns, 6 ft × 1/8 in. stainless steel, packed with 10% SP 2401, 10% SP 2340, and 10% OV-225, all on 80–100 mesh Supelcoport, were used with He as a carrier gas. The appropriate hydrocarbon was used as an internal standard in all chromatographies used for yield calculations. The "usual workup" involved washing organic solvent solutions with water, drying over magnesium sulfate, and evaporating to dryness in vacuo.

(18) H. Breederveld, *Recl. Trav. Chim. Pays-Bas*, **79**, 1197–1202 (1960).

Preparation of 6β-Imidopenicillinate 1(*S*)-Oxides

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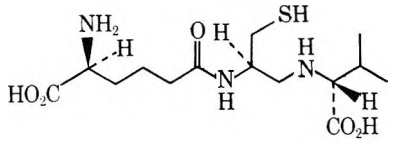
Examples of the as yet unknown 6β-imidopenicillinate 1(*S*)-oxides were prepared and the stereochemistry was proven unambiguously by x-ray diffraction. These substances were thermodynamically stable with respect to the corresponding 1(*R*)-oxides as shown by equilibration via thermal ring opening. The possible significance of these results with respect to the biogenetic relationships of penicillins and cephalosporins is discussed.

The biogenesis of the β-lactam antibiotics, penicillins and cephalosporins,[1] is now generally recognized to derive from Arnstein's tripeptide, L-α-aminoadipyl-L-cysteinyl-D-valine (**1**), since the bioconversion of this substance to penicillins has been reported.[2] The isolation of this substance from *Cephalosporium* sp. has also been reported.[3] The sequence of reactions involved in the conversion of **1** into penicillin N (**2**) and cephalosporin C (**3**) is still unknown; however, two suggestions have been made. Thus, in one case,[4] a priori formation of monocyclic species (**4**) is followed in a branched pathway by the formation of **2** and **3**.[5] An earlier alternative, suggested by Abraham,[6] is the bioconversion of **2** to **3**, but, until recently,[7] this scheme has had little support. The latter is attractive, since the in vitro ring expansion of penicillin sulfoxides to deacetoxycephalosporins is the basis of a commercial production of these compounds.[8] Thus, for example, refluxing methyl 6β-phenoxyacetamidopenicillinate 1(*S*)-oxide (**5**) in xylene with a trace of acid gives the deacetoxycephalosporin (**7**) by way of the sulfenic acid (**6**).[9]



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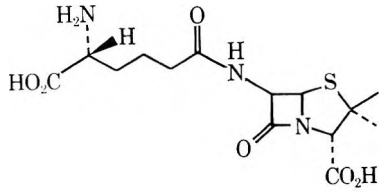

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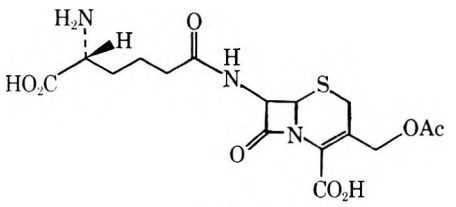

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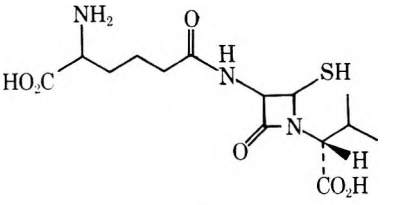

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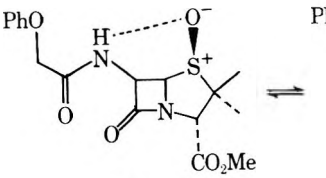

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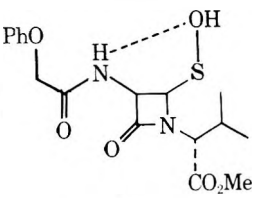

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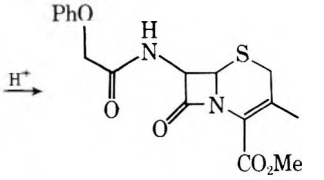

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An immediate objection that could be raised to this hypothesis is that the relatively high temperatures (in the region of 100 °C) required to initiate the thermal ring opening (syn elimination) of **5** to **6** would hardly be available in vivo. An

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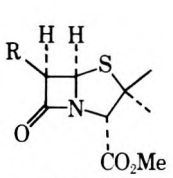
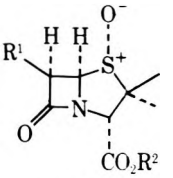
answer to this problem must be sought in the various factors which control the thermal stability of penicillin sulfoxides. Oxidation of methyl 6β-phenoxyacetamidopenicillinate (**8**) gives only the (*S*)-sulfoxide **5**, whereas the similar oxidation of methyl 6β-phthalimidopenicillinate (**9**) yields only the



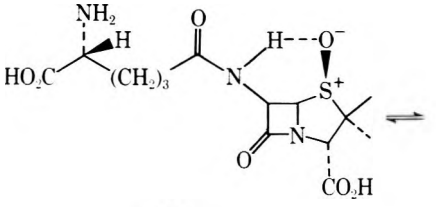
8, R = $NHCOCH_2OPh$
9, R = Phthalimido



10

(*R*)-sulfoxide **10** (R^1 = phthalimido, R^2 = methyl).[10] Presumably, the NH group of **8** directs the reagent to the β face, yielding the (*S*)-sulfoxide, whereas in **9**, with no such group, the sterically more accessible α face provides the epimeric (*R*)-oxide.[11] Thus, the more readily accessible (*S*)-sulfoxides, at least with 6β-amido substituents, cf. **2** and **3**, are the more sterically hindered; however, the demonstrated presence of the hydrogen bond between the sulfoxide and the amide side chain has been suggested[12] as stabilizing these species (**5**) toward the syn elimination to **6**.[13]

Consequently, we argued that if penicillin *N*-(*S*)-sulfoxide **11** were a biointermediate for deacetoxycephalosporin C (**13**),



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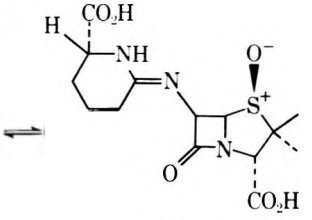

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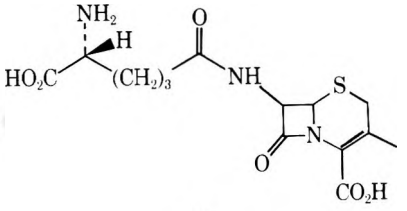

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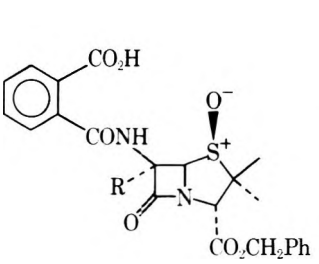
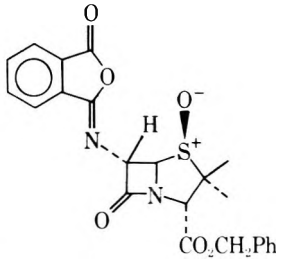
a suggestion which is in stereochemical accord with the derivation of both penicillins and cephalosporins from chiral methyl-labeled valine,[14] then some means must exist for "switching off" this stabilizing H bond. Such a mechanism could involve the α-aminoadipyl side chain, via cyclic amidine formation, as **12**,[15] in which the steric overcrowding of the sulfoxide might accelerate the ring-opening elimination sufficiently to allow its occurrence under physiological conditions. To test this hypothesis, it was necessary to prepare a penicillin (*S*)-oxide with a 6β side chain containing no NH group and to study the facility of ring opening. To date there is no report of such compounds.

Condensation of benzyl 6β-aminopenicillinate 1(*S*)-oxide with phthalic anhydride cleanly afforded the phthalamic acid **14a** (R = H) which with DCC gave the 6α-isoimidopenicillin 1(*S*)-oxide (**15**) instead of the expected 6β-isoimide **16a** (R = H). Interestingly, a similar sequence conducted on the parent benzyl 6β-aminopenicillinate gave the 6β-isoimido product **18** via the phthalamic acid **17**. Clearly, the epimerization of



14a, R = H
b, R = Me



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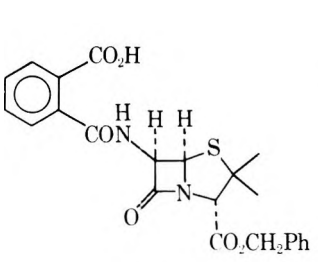

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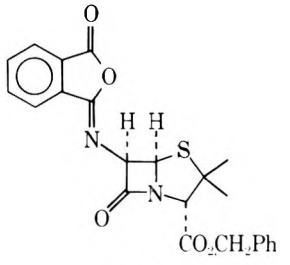

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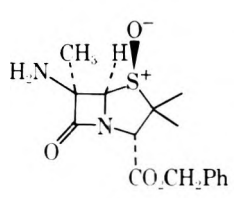
C-6 during dehydration of the phthalamic acid **14a** (R = H) is consequent on the presence of the 1(*S*)-oxide function in **14a** (R = H), although it is not clear whether this effect is steric or the result of an inductive acidification of the 6α-hydrogen.



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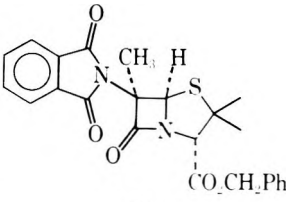

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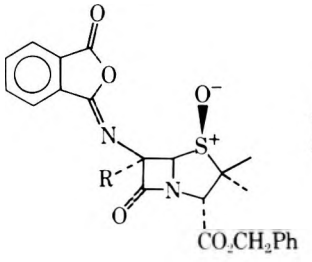
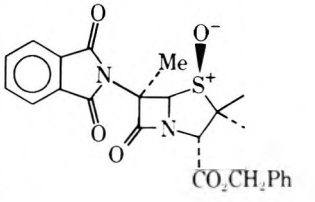
In order to avoid this unwanted epimerization, we replaced the 6α-hydrogen by a methyl group. Thus, the known benzyl 6β-amino-6α-methylpenicillinate[16] was oxidized to the (*S*)-sulfoxide **19** and converted sequentially to the phthalamic acid **14b** (R = Me) and the 6β-isoimide **16b** (R = Me). Unfortunately, the spectral properties of **16b** (R = Me) did not allow



16a, R = H
b, R = Me



20

unambiguous assignment of sulfoxide stereochemistry, which was critical since if the proposed hypothesis of instability of such 6β-imido 1(*S*)-oxides were correct then thermal ring opening at the ambient temperature of the dehydration could possibly have inverted this sulfoxide stereochemistry. If this were true, it would require a sulfenic acid intermediate, cf. **6**, which should be detectable by its known chemistry. Consequently, the phthalamic acid **14b** (R = Me) was treated with DCC in the presence of excess norbornadiene, a reagent known to intercept sulfenic acids.[17] However, no adduct was found

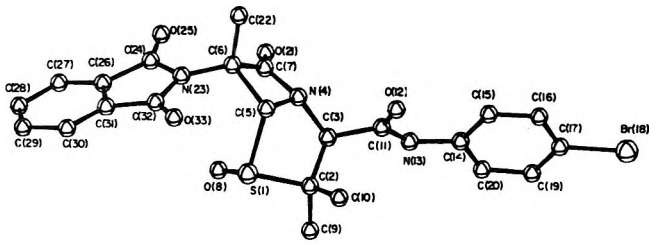
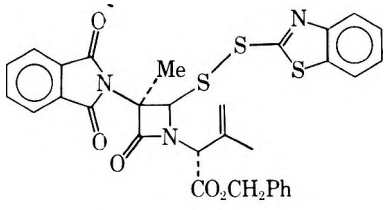


Figure 1. A computer-generated drawing of **23.**

and, interestingly, the presence of diene effected a change in the mode of ring closure to the imide **20.** The origin of this effect is unknown. That the sulfoxide **20** is the thermodynamically more stable was shown by its reisolation, unchanged, after prolonged refluxing in toluene. Treatment of **20** with 2-mercaptobenzthiazole in refluxing benzene gave, via trapping of the sulfenic acid, the β-lactam **21.** Reduction



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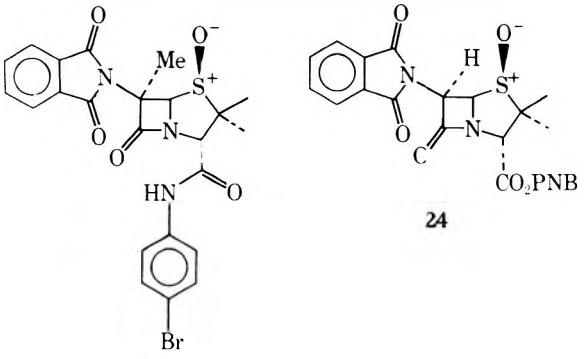
of **20** with phosphorus tribromide gave the corresponding sulfide **22** which was reoxidized with peracid to the same sulfoxide **20.** From this chemical evidence, one would infer that the configuration of the sulfoxide in **20** is *R* based on analogy with the known oxidation chemistry of 6β-phthalimidopenicillin esters.[18]

Removal of the benzyl ester of **20** by catalytic hydrogenolysis gave the derived acid, which with *p*-bromoaniline gave the amide **23** via the mixed anhydride synthesis. The structure



23

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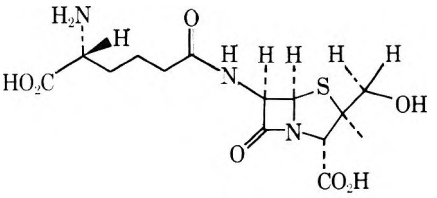
and configuration of **23** was determined by an x-ray diffraction analysis, proving the sulfoxide to be in the *S* configuration. Figure 1 is a perspective drawing of the final x-ray model of **23.** All bond distances and angles agree well with generally accepted values and no abnormally short intermolecular contacts were observed save one intermolecular NH···O–S distance of 2.87 Å. Thus, **23** and therefore **20** and **16b** (R = Me) are first examples of 6β-imidopenicillin (*S*)-sulfoxides. They are also the more stable of the epimers at sulfur as shown by the equilibration experiments.

In the course of some other work, it was found that prolonged refluxing of *p*-nitrobenzyl 6β-phthalimidopenicillinate 1(*R*)-oxide (**10,** R^1 = phthalimido, R^2 = *p*-nitrobenzyl) in toluene gave a highly insoluble substance (90%) which proved to be the corresponding 1(*S*)-oxide **24,** whose NMR spectrum showed the presence of two cis-oriented protons at C-5 and C-6. This supports the idea that the 6β-imidopenicillinate 1(*S*)-oxides are the more stable isomers both in the 6α-methyl and the 6α-hydrogen series. The same order of stability apparently is also true in the 6α-imidopenicillinates as was shown in the work of Spry,[19] who demonstrated that the equilibrium between the (*R*)- and (*S*)-sulfoxides of methyl 6-epiphthalimidopenicillinate favors the (*S*)-sulfoxide. An extrapolation of this finding is that the order of stability of the sulfoxides, 1(*S*) > 1(*R*), is not the result of steric factors, since particularly with a 6β-imido function of the 1(*S*) series is far more hindered, nor is it the result of hydrogen bonding since these species contain no such H bond.

With respect to our original hypothesis concerning the possible in vivo conversion of **11** to **13** via **12,** it is evident from the results presented above that a 1(*S*)-oxide such as **12** is not, at least on chemical grounds, a likely, labile, intermediate in this hypothetical transformation. In view of the known facility[20] of conversion of β-chloromethylpenams into cephems, it therefore seems reasonable to consider the β-hydroxymethylpenicillin N (**25**) as an alternative chemically reasonable precursor to deacetoxycephalosporin C in vivo.[21]



25

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus or on a Kofler Micro Hot Stage block and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer Model 700 infrared spectrophotometer and were calibrated against polystyrene. Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 or a Perkin-Elmer R-20B or R-22 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane with the notations giving the multiplicity of the signal, the coupling constant if applicable, and the number of protons. Spin multiplicity is given by s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E spectrometer.

Silica gel for column chromatography was Merck silica gel 60, no. 7734. Analytical thin-layer chromatography was performed on Baker-flex silica gel IB-F or Merck precoated silica gel TLC plates 60F-254. Preparative thin-layer separations were carried out on Merck silica gel GF 254 (type 60), no. 7730, on 200 × 200 × 1.25 mm layers.

Benzyl 6β-(*o*-Carboxybenzamido)penam-3α-carboxylate 1β-Oxide (14a). To a solution of benzyl 6β-aminopenam-3α-carboxylate 1β-oxide (223 mg, 0.69 mmol) in dichloromethane (4 mL) was added a solution of phthalic anhydride (103 mg, 0.69 mmol) in tetrahydrofuran (4 mL). After stirring for 2 h, the solution was concentrated in vacuo leaving **14a** in quantitative yield (320 mg) as a white foam: NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.56 (s, 3 H), 4.67 (s, 1 H), 5.21 (s, 2 H), 5.33 (d, *J* = 4 Hz, 1 H), 6.23 (dd, *J* = 4, 10 Hz, 1 H), 7.40 (s, 5 H), 7.40–8.05 (m, 5 H), 10.38 (br s, 1 H); IR ($CDCl_3$) 3450–2950, 1780, 1740, 1720 (br) cm^{-1}.

Benzyl 6α-Isophthalimidopenam-3α-carboxylate 1β-Oxide (15). To a solution of DCC (143 mg, 0.69 mmol) in tetrahydrofuran (4 mL) was added a solution of **14a** (320 mg, 0.69 mmol) in tetrahydrofuran (3 mL), and the resulting solution was stirred at room temperature for 18 h and then concentrated to dryness in vacuo. Ethyl acetate (5 mL) was added to the residue and the suspended solid removed by filtration. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as eluant; R_f 0.4), affording **15** in 67% yield (210 mg) as a yellow syrup: NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.71 (s, 3 H), 4.55 (s, 1 H), 5.05 (d, *J* = 1 Hz, 1 H), 5.15 (d, *J* = 1 Hz, 2 H), 5.25 (d, *J* = 1 Hz, 1 H), 7.22 (s, 5 H), 7.45–7.92 (m. 4 H); IR ($CHCl_3$) 1810, 1780, 1740, 1710 1695 cm^{-1}.

Benzyl 6β-(*o*-Carboxybenzamido)penam-3α-carboxylate (17). To a solution of 6-APA benzyl ester (61 mg, 0.2 mmol) in tetrahy-

drofuran (2 mL) was added a solution of phthalic anhydride (30 mg, 0.2 mmol) in tetrahydrofuran (2 mL). After stirring for 105 min, the solution was concentrated in vacuo, leaving **17** in quantitative yield (90 mg) as a white foam: NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.60 (s, 3 H), 4.43 (s, 1 H), 5.20 (s, 2 H), 5.5–5.92 (m, 2 H), 7.00 (d, J = 8 Hz, 1 H), 7.35 (s, 5 H), 7.40–8.00 (m, 4 H), 8.77 (br s, 1 H); IR ($CHCl_3$) 3500–2950, 1780, 1740, 1700 cm^{-1}.

Benzyl 6β-Isophthalimidopenam-3α-carboxylate (18). To a solution of DCC (41 mg, 0.2 mmol) in tetrahydrofuran (5 mL) was added a solution of **17** (90 mg, 0.2 mmol), and the resulting mixture was stirred at room temperature for 18 h and then concentrated in vacuo. Ethyl acetate (5 mL) was added and the suspended solid was removed by filtration. The filtrate was concentrated to dryness in vacuo, leaving a syrup. Purification by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as eluant; R_f 0.5) afforded **18** in 84% yield (73 mg) as a yellow syrup: NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.67 (s, 3 H), 4.53 (s, 1 H), 5.23 (s, 2 H), 5.60, 5.73 (AB q, J_{AB} = 4 Hz, 2 H), 7.40 (s, 5 H), 7.65–8.05 (m, 4 H); IR ($CHCl_3$) 1805, 1780, 1735, 1700 cm^{-1}.

Benzyl 6β-Amino-6α-methylpenam-3α-carboxylate 1β-Oxide (19). Benzyl 6β-amino-6α-methylpenicillinate (106 mg, 0.32 mmol) was dissolved in dichloromethane (4 mL) and cooled to −15 °C. A solution of *m*-chloroperbenzoic acid (56 mg, 0.32 mmol) in dichloromethane (2 mL) was added dropwise, and the resulting solution was stirred in the cold for 90 min and at room temperature for 40 min. The mixture was concentrated in vacuo and the residue was redissolved in ethyl acetate. This solution was washed with saturated sodium bicarbonate and brine and was dried ($MgSO_4$) and concentrated in vacuo, leaving **19** in 94% yield (95 mg) as a white foam: NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.70 (s, 3 H), 1.75 (s, 3 H), 2.50 (br s, 2 H), 4.55 (s, 2 H, H-3 and H-5), 5.10 (d, J = 2 Hz, 2 H), 7.3 (s, 5 H); IR ($CHCl_3$) 3500, 3410, 1780, 1740 cm^{-1}.

Benzyl 6β-(*o*-Carboxybenzamido)-6α-methylpenam-3α-carboxylate 1β-Oxide (14b). **19** (108 mg, 0.32 mmol) was dissolved in dichloromethane (2 mL) and to this solution was added a solution of phthalic anhydride (48 mg, 0.32 mmol) in tetrahydrofuran (2 mL). The resulting solution was stirred at room temperature for 2 h and then concentrated in vacuo, leaving **14b** in quantitative yield (155 mg) as a pale-yellow foam: NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.65 (s, 3 H), 1.95 (s, 3 H), 4.50 (s, 1 H), 4.85 (s, 1 H), 5.20 (d, J = 2 Hz, 2 H), 7.20 (s, 5 H), 7.20–8.00 (m, 4 H), 9.00 (br s, 1 H); IR ($CHCl_3$) 3500–2900, 1780, 1735, 1700 cm^{-1}.

Benzyl 6β-Isophthalimido-6α-methylpenam-3α-carboxylate 1β-Oxide (16b). 14b (155 mg, 0.32 mmol) was dissolved in tetrahydrofuran (12 mL) and added dropwise to a stirring solution of DCC (67 mg, 0.32 mmol) in tetrahydrofuran (20 mL), and the resulting mixture was stirred at room temperature for 18 h and then concentrated in vacuo to dryness. To the residue was added ethyl acetate (5 mL) and a suspended solid was removed by filtration. The filtrate was concentrated in vacuo. Purification of the residue by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.2) afforded **16b** in 48% yield (72 mg) as a pale-yellow foam: NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.65 (s, 3 H), 2.00 (s, 3 H), 4.60 (s, 3 H), 5.00 (s, 1 H), 5.20 (d, J = 2 Hz, 2 H), 7.20 (s, 5 H), 7.40–8.00 (m, 4 H); IR ($CHCl_3$) 1790 (br), 1740 cm^{-1}.

Benzyl 6β-Phthalimido-6α-methylpenam-3α-carboxylate 1β-Oxide (20) from 14b. 14b (63 mg, 0.13 mmol) was dissolved in tetrahydrofuran (4 mL) and was added dropwise to a stirring solution containing DCC (27 mg, 0.13 mmol) and norbornadiene (240 μL, 2.6 mmol) in tetrahydrofuran (7 mL). The resulting solution was stirred for 15 h and then concentrated in vacuo. To the residue was added ethyl acetate (5 mL), and the suspended solid was removed by filtration. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.3) affording **20** in 86% yield (52 mg) as a white amorphous solid: mp 180–183 °C (dec); NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.65 (s, 3 H), 2.10 (s, 3 H), 4.70 (s, 1 H), 5.00 (s, 1 H), 5.30 (d, J = 2 Hz, 2 H), 7.40 (s, 5 H), 7.60–7.90 (m, 4 H); IR ($CHCl_3$) 1790, 1735 (br) cm^{-1}.

(3*R*,4*R*)-1-[(1*R*)-Benzoxycarbonyl-2-methyl-2-propenyl]-3-phthalimido-3-methyl-4-(benzthiazole-2-dithio)-2-azetidinone (21). A solution of **20** (46 mg, 0.1 mmol) and 2-mercaptobenzthiazole (17 mg, 0.1 mmol) in dry benzene (4 mL) was refluxed under nitrogen for 3 h and then concentrated in vacuo. Preparative TLC on silica gel (2:1 benzene–ethyl acetate as the eluant; R_f 0.6) afforded **21** in 60% yield (37 mg) as a clear, colorless syrup: NMR ($CDCl_3$) δ 2.15 (s, 3 H), 2.25 (s, 3 H), 5.05 (s, 1 H), 5.25 (br d, 4 H, $-OCH_2Ph$ and $C{=}CH_2$), 5.50 (s, 1 H), 7.30 (s, 5 H), 7.30–8.00 (m, 8 H); IR ($CHCl_3$) 1770, 1735, (br) cm^{-1}. The starting sulfoxide was also isolated in 30% yield (14 mg).

Benzyl 6β-Phthalimido-6α-methylpenam-3α-carboxylate (22). The sulfoxide **20** (40 mg, 0.086 mmol) was dissolved in dry DMF (1 mL) and cooled under N_2 to −5 °C. Phosphorus tribromide (40 μL, 5 equiv) was added, and the resulting solution was stirred in the cold for 10 min and then poured into saturated sodium bicarbonate (10 mL). This was extracted with ethyl acetate, and the organic phase was washed with 1 N HCl and saline and dried ($MgSO_4$). Concentration in vacuo left a syrup (43 mg). Purification by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.5) afforded **22** in 65% yield (25 mg) as a clear, colorless syrup: NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.47 (s, 3 H), 1.95 (s, 3 H), 4.53 (s, 1 H), 5.13 (s, 2 H), 5.50 (s, 1 H), 7.30 (s, 5 H), 7.68 (m, 4 H).

Benzyl 6β-Phthalimido-6α-methylpenam-3α-carboxylate 1β-Oxide (20) from Oxidation of 22. To a −15 °C solution of **22** (22 mg, 0.049 mmol) in dichloromethane (1 mL) was added a solution of *m*-chloroperbenzoic acid (8 mg, 0.049 mmol) in dichloromethane (2 mL). The resulting solution was stirred in the cold for 1 h and then at room temperature for 45 min. The solution was washed with saturated sodium bicarbonate and saline and then was dried ($MgSO_4$) and concentrated in vacuo, leaving a foam. Purification by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.3) afforded the sulfoxide **20** in 67% yield (15 mg) as a foam. NMR and IR spectra were identical to those for **20** obtained from the phthalamic acid **14b**.

6β-Phthalimido-6α-methylpenam-3α-*p*-bromocarboxanilide 1β-Oxide (23). To a solution of **20** (255 mg, 0.546 mmol) in glacial acetic acid (10 mL) and chloroform (10 mL) was added 255 mg of palladium on charcoal. This mixture was shaken mechanically under 1 atm of H_2 at room temperature for 4 h and then filtered. Chloroform was removed from the filtrate in vacuo and the remaining acetic acid solution was freeze-dried, leaving the acid as a white solid.

To a solution of the acid (75 mg, 0.199 mmol) in dry THF (6 mL) was added triethylamine (28 μL, 0.199 mmol) and the resulting solution was cooled to −5 °C. Ethyl chloroformate (16 μL, 0.199 mmol) was added dropwise to the stirring cold solution, and the resulting mixture was stirred in the cold for 15 min and then for 20 min while warming to room temperature. The turbid solution was recooled to 0 °C and *p*-bromoaniline (34 mg, 0.199 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred at room temperature for 85 min and then was concentrated in vacuo, leaving a foam. A chloroform solution of this product was washed with water, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated in vacuo to dryness. Preparative thin-layer chromatography on silica gel (1:1 benzene–ethyl acetate as eluant) afforded **23** as an amorphous solid (76 mg, 72%): NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.55 (s, 3 H), 2.13 (s, 3 H), 4.50 (s, 1 H), 5.05 (s, 1 H), 7.40 and 7.62 (AB q, J_{AB} = 7 Hz, 4 H), 7.75 (m, 4 H); IR ($CHCl_3$) 3400, 1805, 1715 cm^{-1}. Crystals for x-ray were obtained (mp 210–212 °C (corrected) from acetone–petroleum ether by the "vapor diffusion" method.

X-Ray Analysis of 6β-Phthalimido-6α-methylpenam-3α-*p*-bromocarboxanilide 1β-Oxide (23). The crystals of **23** belonged to the unambiguously determined space group $P_c2_12_12_1$. Accurate lattice dimensions were obtained from a least-squares fit of 15 2θ values between 35.0° and 45.0°. The cell constants are a = 9.342 (4), b = 13.750 (7), and c = 18.635 Å. A calculated (Z = 4) and observed density of 1.46 g/cm³ indicated one molecule of composition $C_{23}H_{20}O_5N_3SBr$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114.1°$ were recorded in the θ scan mode using a computer-controlled four-circle diffractometer and graphite monochromated Cu Kα x-rays (1.54178 Å). Of the 1855 reflections surveyed, 1628 (88%) were judged observed [$I \geq 3\sigma(I)$] after correction for Lorentz polarization and background effects.

A sharpened three-dimensional Patterson[22] was readily deconvoluted to yield the bromine and sulfur position. A subsequent Fo synthesis revealed the rest of the nonhydrogen atoms. Full-matrix, least-squares refinements with anisotropic temperature factors for all nonhydrogen atoms have converged to a standard crystallographic residual of 0.050 for the observed reflections. Additional crystallographic details such as the positional and thermal parameters, bond distances and angles, and observed and calculated structure factors are presented in Tables I–IV (Supplementary Material).

p-Nitrobenzyl 6β-Phthalimidopenicillinate 1(S)-Oxide (24). Toluene (50 mL) was dried by binary distillation for 2 h. Heat was removed temporarily and *p*-nitrobenzyl 6β-phthalimidopenicillinate 1(*R*)-oxide (**10**, R^1 = phthalimido; R^2 = *p*-nitrobenzyl, 2.0 g (5 mM), was added. The solution was refluxed for 6 h, during which time a crystalline and highly insoluble solid was formed. It was filtered and rinsed with acetone and vacuum dried to give the 1(*S*)-oxide **24**, mp 204 °C (dec), in 90% yield. Proton NMR (100 MHz, Me_2SO-d_6) δ 1.20 (s, 3 H), 1.51 (s, 3 H), 4.63 (s, 1 H), 5.41 (s, 2 H), 5.68 (AB q, 2 H, J = 4.5 and 8.0 Hz), 7.72 (d, 2 H, J = 9.5 Hz), 8.27 (d, 2 H, J = 9.5 Hz) and

7.88 (ms, 4 H); IR (mull) 1790, 1780, 1720, 1515, 1460, 1380, 1345, 1270 cm^{-1}; ^{13}C NMR (Me_2SO-d_6, ref Me_4Si) δ 17.8, 19.0 (2-CH_3), 72.1 (C-2), 65.9 (C-3), 72.7 (C-5), 56.1 (C-6).[23]

In the combined solution of the toluene filtrate and acetone rinse, a 2–3% solid was recovered, which was identical to an authentic sample of the *p*-nitrobenzyl ester of 3-hydroxyl-3-methyl-7β-phthalimidocephalosporin.

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Registry No.—**10** (R^1 = phthalimido; R^2 = *p*-nitrobenzyl, 35160-70-4; **14a**, 65102-78-5; **14b**, 65102-79-6; **15**, 65102-80-9; **16b**, 65102-81-0; **17**, 65102-82-1; **18**, 65102-83-2; **19**, 65102-84-3; **20**, 65102-85-4; **21**, 65102-86-5; **22**, 65102-87-6; **23**, 65102-88-7; **24**, 65165-49-3; benzyl 6β-aminopenam-3α-carboxylate β-oxide, 65165-50-6; phthalic anhydride, 85-44-9; benzyl 6β-aminopenam-3α-carboxylate, 3956-31-8; benzyl 6β-amino-6α-methylpenicillinate, 36273-78-6; 2-mercaptobenzthiazole, 149-30-4.

Supplementary Material Available. Tables of atomic coordinates, temperature factors, bond angles, and bond distances (3 pages). Ordering information is given on any current masthead page.

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Haloaziridines. 2. Synthesis and Pyrolysis of Some *gem*-Dichloroaziridines[1,2]

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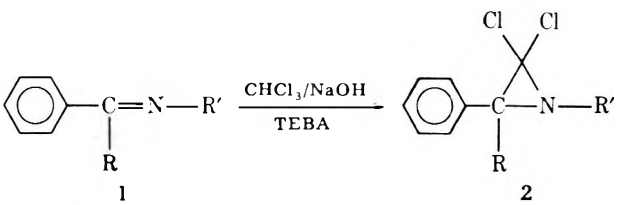
An improved synthesis of *gem*-dichloroaziridines from imines and dichlorocarbene is reported using chloroform, sodium hydroxide, and triethylbenzylammonium chloride to generate the dichlorocarbene. The preparation of some *gem*-dichloroaziridines from phenyl(trihalomethyl)mercury reagents is reported and the previous reports are examined. The *gem*-dichloroaziridines prepared under these latter conditions are subject to a phenylmercuric halide catalyzed ring-opening reaction. A pyrolysis study delineated the factors controlling the ring-opening reaction and demonstrated the synthetic utility of this reaction.

The preparation of *gem*-dichloroaziridines has been accomplished by the addition of dichlorocarbene to the carbon–nitrogen double bond of an imine. The dichlorocarbene in this reaction has been generated from the reaction of chloroform, hexachloroacetone, or ethyl trichloroacetate with the appropriate base.[4] Recently, Seyferth has reported the preparation of 1,3-diphenyl-2,2-dichloroaziridine in low yield using $PhHgCBrCl_2$ to generate the dichlorocarbene.[5] Makosza has reported the generation of dichlorocarbene from chloroform and aqueous sodium hydroxide using a phase-transfer agent.[6] These phase-transfer catalyzed two-phase reactions have been used in a variety of reactions in addition to generating dichlorocarbene. The chemistry of these types of reactions has been recently reviewed.[7]

Phase-Transfer Preparations. We have examined the preparation of *gem*-dichloroaziridines from imines (**1**) using



1 **2**

aqueous sodium hydroxide, chloroform, and triethylbenzylammonium chloride (TEBA) as the phase-transfer agent. The isolated yields for this catalytic method are contrasted to the best yield obtained from the other reported methods

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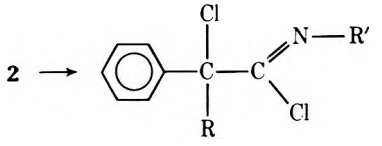
Table I. Preparation of *gem*-Dichloroaziridines

Registry no.	Compd	R	R′	Catalytic[a]	Other	Time[b]	Solvent[c]	Lit.[d]
3543-98-4	**2a**	Hydrogen	Phenyl	74	80[e]	40	Hexane	*f*
31528-97-9	**2b**	Ethyl	Phenyl	76	56	30	Hexane	1
972-14-5	**2c**	Phenyl	Phenyl	72[g]	63	40	Hexane–EtOAc	*h*
31528-96-8	**2d**	Phenyl	Benzyl	72	65[i]	40	EtOAc	1
31528-95-7	**2e**	Hydrogen	1-Naphthyl	72	44	40	Hexane–EtOAc	1
65016-16-2	**2f**	Methyl	1-Naphthyl	74	45	50	EtOAc	*a*
25252-58-8	**9**			88	53[j]	180	Hexane[a]	5

[a] See Experimental Section. [b] Reaction time in minutes. [c] Solvent for crystallization. [d] Literature reference for the best reported preparation of the aziridine by other methods. [e] Normal yields are ~50–60%; see ref 1. [f] R. E. Brooks, J. O. Edwards, G. Levey, and F. Smyth, *Tetrahedron*, **22**, 1279 (1966). [g] Yield of the α-chloroimidoyl chloride **3c**. [h] K. Ichimura and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 1933 (1967). [i] Normal yields are ~4%; see ref 1. [j] This yield is based on the carbene.

for the preparation of *gem*-dichloroaziridines in Table I. In all cases the yields are about equal to or superior to the best previously reported preparations of *gem*-dichloroaziridines. In addition, the catalytic method has the advantage of being quick, convenient, and inexpensive. The reaction is exothermic and precautions should be taken to maintain the temperature at 40 °C in large-scale preparations.[6] Graefe has reported high yields of phenyl substituted 1,3-diphenyl-2,2-dichloroaziridines (**2a**) using the catalytic method at temperatures between 0 and 20 °C.[8]

Longer reaction times failed to significantly improve the yields reported in Table I and resulted in lower isolated yields of **2b** and **2f** due to the instability of these aziridines to longer reaction times. Aziridine **2c** was not stable to the reaction conditions and rearranged to the α-chloroimidoyl chloride **3c** which was isolated in 72% yield. This aziridine could be prepared in 71% yield via the catalytic method using lower temperatures and a longer reaction period.



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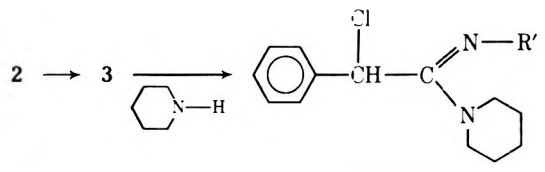
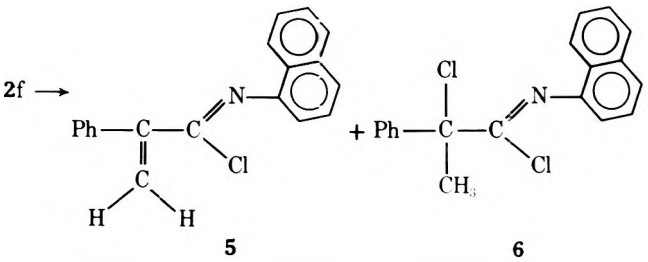
Pyrolysis Studies. In our investigations of the synthetic utility of *gem*-dichloroaziridines, it was necessary to determine the thermal stability of some of these compounds. There were two isolated reports of pyrolysis reactions in the literature; aziridine **2a** afforded **3a** in hot toluene (no reported yield)[9] and **2c** was converted to **3c** (71% yield) after 1 h in hot xylene.[10] Of the aziridines in Table I, the pyrolysis of **2a** and **2e** were conveniently monitored via NMR spectrometry by following the loss of the aziridinyl proton at δ 3.6 and the appearence of the benyzlic proton of **3** near δ 5.8. Aziridine **2e** was quantitatively converted in 4 h while **2a** was 83% rearranged after 24 h.[11] Longer reaction times in the latter reaction resulted in significant decomposition. These pyrolysis reactions have synthetic utility since quenching the reaction with piperidine afforded high yields of the α-chloroamidines **4a** and **4e**.



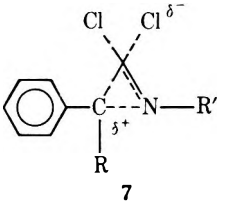
4a and 4e

The toluene pyrolysis of **2c** for 1 h afforded a 78% yield of **3c**. The pyrolysis of **2d** and **2f** was monitored via NMR spectrometry by following the loss of the aziridinyl methylene and methyl signals, respectively. Aziridine **2d** was quantatively converted in 8 h while **2f** required 3 h and afforded a 1:3 mixture of **5** and **6**.[11] In pyridine, a more polar solvent, the pyrolysis of **2f** required 1 h and a 45:55 mixture of **5** to **6** was observed while a 2:3 mixture of the amides corresponding to the hydrolysis of **5** and **6** was obtained in water after 15 min.[11]



5 **6**

The order of decreasing pyrolysis rates for the 1-aryl substituted *gem*-dichloroaziridines is **2c** > **2f** > **2e** > **2a** and roughly correlates with decreasing strain and decreasing carbonium ion stability. The difference in reactivity between **2a** and **2e** is attributed to the greater electron-donating ability of naphthyl in stabilizing the transition state since both aziridines give rise to the same carbonium ion. These data are consistent with transition state **7** which is also supported by recently reported observations.[12]



7

Phenyl(trihalomethyl)mercury Preparations. We have also examined the synthetic utility of some phenyl(trihalomethyl)mercury reagents as the carbene source in the preparation of *gem*-dichloroaziridines. These thoroughly studied Seyferth reagents undergo pyrolysis to yield dihalocarbene and the phenylmercuric halide.

$$PhHgCX_3 \rightarrow PhHgX + \dot{X}C\dot{X}$$

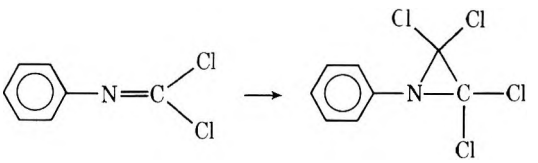
They have been used to prepare *gem*-dihalocyclopropanes and have the advantage of not requiring basic reaction conditions.[13] Recently, Seyferth et al. have reported the use of these reagents for the addition of dichlorocarbene to the C=N, C=S, C=O, and N=N.[14] Seyferth reported the reaction of benzylideneaniline (**1a**) with phenyl(bromodichloromethyl)-mercury lead to tar formation in benzene[15] and a trace of **2a** and tar in carbon tetrachloride.[5] The inability of this reagent to convert the imine to the *gem*-dichloroaziridine was attributed by Seyferth to nucleophilic attack of the imine ni-

Table II. Stability Studies of 1,3-Diphenyl-2,2-dichloroaziridine (2a)

Reactant(s)	Conditions	Time[a]	NMR analysis	
			% aziridine	% imidoyl chloride
Benzene[b]	Reflux	48	100[c]	*d*
CCl_4/PhHgCl[e,f]	r.t.[g]	48	100[c]	*d*
Benzene/PhHgCl	Reflux	24	36	64
DME/PhHgCl	r.t.[g]	48	98[c]	2
Benzene/PhHgBr	Reflux	2	100	*d*
DME/NaI	r.t.[g]	48	100	*d*

[a] Reaction time in hours. [b] Similar results were obtained for CCl_4 (48 h) and DME (18 h). [c] Recovered >85%. [d] The imidoyl chloride could not be detected. [e] A saturated solution. [f] Comparable results were obtained for PhHgBr. [g] Room temperature.

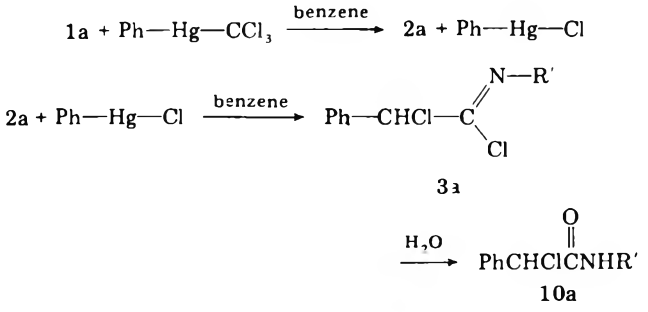
trogen at mercury giving rise to tar formation. Using a less nucleophilic imine such as phenylcarbonimidoyl dichloride (8), Seyferth obtained the tetrachloroaziridine **9** in 53% yield



8 **9**

based on the mercurial.[5] We obtained the same aziridine in 88% yield using the phase-transfer reaction.[11]

Our initial attempts to prepare *gem*-dichloroaziridines from the Seyferth reagents involved the pyrolysis of a 1:1 mixture of **1a** and phenyl(trichloromethyl)mercury in benzene for 48 h. The product was a red oil which was identified as the imidoyl chloride **3a** by its NMR spectrum and by conversion to the amide **10a** in 22% yield. Using a fourfold excess of the mercurial afforded the amide in 68% yield. The isolation of the amide strongly suggested the intermediacy of **2a** since the pyrolysis of **2a** to **3a** has been established. In hot benzene, **2a** was stable for 48 h; however, in the presence of phenylmercuric chloride, **2a** was quantitatively converted to **3a** (via NMR) establishing the phenylmercuric chloride catalyzed ring opening reaction. Consequently, the use of phenyl(trihalomethyl)mercury reagents should be limited by the thermal stability of the *gem*-dichloroaziridine and its stability toward the phenylmercuric halide produced in the reaction and/or the phenyl(trihalomethyl)mercury reagent. The results of some stability studies with the rather stable aziridine **2a** are presented in Table II. These results tend to rule out the pyrolysis of phenyl(trichloromethyl)mercury for the preparation of these *gem*-dichloroaziridines.



Treatment of phenyl(trichloromethyl)mercury with sodium iodide and dry dimethoxyethane (DME) at room temperature affords dichlorocarbene[16] and circumvents the pyrolytic ring opening reaction. Under these conditions, **1d** was converted to **2d** in 98% yield, the highest yield ever reported for a *gem*-dichloroaziridine preparation. Application of this reaction to **1a** and **1e** failed to yield the aziridine; however, NMR analysis established the presence of the rearrangement products **3a** and **3e**. Chromatography over alumina afforded the amide **10a** in 59% yield. Aziridines **2a** and **2e** were stable to phenylmercuric chloride under these conditions; however, it was established that the phenylmercuric iodide formed in the reaction catalyzed the ring opening.

Seyferth's attempted preparation of *gem*-dichloroaziridines using phenyl(bromodichloromethyl)mercury required even milder conditions than those for phenyl(trichloromethyl)mercury, albeit he reported tar formation and only a trace of **2a**.[5] Based on our high percent conversions of imines **1a, 1d,** and **1e** to the corresponding aziridine or their rearrangement products with phenyl(trichloromethyl)mercury and the stability studies (Table II), we felt that these earlier reports should be examined. Duplicating this experimental by pyrolysis of a 1:1 mixture of phenyl(bromodichloromethyl)mercury and **1a** in benzene for 2 h afforded phenylmercuric bromide (87%) and a dark oil. NMR analysis of this oil detected a strong aziridinyl proton signal at δ 3.58 and the impure aziridine was isolated in 40% yield after several recrystallizations from hexane.[17] Doubling the concentration of the mercurial failed to increase the aziridine yield. Using phenyl(bromodichloromethyl)mercury and NaI at 0 to −10 °C in DME also afforded **2a** in low yield. Consequently, phenyl(bromodichloromethyl)mercury can be used to prepare *gem*-dichloroaziridines from imines, although the yields are relatively low and the isolation and purification of the aziridine is considerably more difficult than the conventional methods.

Experimental Section

All melting points are uncorrected and were determined on a Mel-Temp melting point apparatus. The nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A or T-60A spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined in potassium bromide on a Perkin-Elmer 137 spectrophotometer. The microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Toluene, *p*-xylene, and DME were purified by distillation from $LiAlH_4$, while pyridine and piperidine were distilled from potassium hydroxide pellets prior to use.

Preparation of *gem*-Dichloroaziridines. General Procedure. The basic procedure of Makosza and Wawrzyniewicz was used.[6] To a mixture of imine (0.01 mol), chloroform[18] (8 mL, 0.10 mol) and triethylbenzylammonium chloride (0.1 g) is added a 50% solution of sodium hydroxide (20 mL). The mixture is vigorously stirred via a magnetic stirrer for ~30 to 60 min at 40 °C. The mixture is extracted with 3 × 20 mL portions of methylene chloride; the combined extracts are washed once with water (20 mL) and dried ($MgSO_4$). The mixture is filtered and the solvent removed in vacuo to afford the crude aziridine. The aziridines are purified by crystallization and the reaction times, yields, and solvents for crystallization are summarized in Table I.

1-Phenyl-2,2,3,3-tetrachloroaziridine (9). The above catalytic procedure was adapted for larger scale preparations by replacing the magnetic stirrer with a high speed mechanical stirrer and the temperature was maintained at 30 °C by external cooling. To a mixture of 10.24 g (0.0588 mol) of phenylcarbonimidoyl dichloride, chloroform (100 mL), and ~0.1 g of TEBA was added a 50% solution of sodium hydroxide (200 mL). The reaction was vigorously stirred and the

temperature maintained at 30 °C for 3 h. The mixture was extracted with 4 × 30 mL of methylene chloride; the combined extracts were washed with water (3 × 30 mL) and dried ($MgSO_4$). The mixture was filtered and the solvent removed in vacuo. 1-Phenyl-2,2,3,3-tetrachloroaziridine crystallized on standing overnight to afford 13.25 g (87%), mp 37–40 °C. Recrystallization from hexane afforded the pure aziridine, mp 39–40 °C (lit.[5] 38–40 °C).

1-(1-Naphthyl)-3-methyl-3-phenyl-2,2-dichloroaziridine (2f). Using the above general procedure, **2f** was obtained in 74% yield, while the yield from the sodium methoxide–chloroform method[1] was 45%: mp 109–110 °C; NMR ($DCCl_3$) δ 8.3–7.1 (m, 12, aromatic) and 1.8 (s, 3, CH_3).

Anal. Calcd for $C_{19}H_{15}Cl_2N$: C, 69.52; H, 4.62; N, 4.27. Found: C, 69.57; H, 4.69; N, 4.19.

Pyrolysis Reactions. General Procedure. The aziridines (0.1–0.5 g) were placed in a two-necked flask fitted with condenser and septum or stopper. The condenser was connected to a nitrogen-vacuum double manifold and a nitrogen atmosphere was introduced by the standard method.[19] The solvent was introduced via syringe through the septum or by removing the stopper while maintaining a positive nitrogen pressure. The magnetically stirred solution was heated at the reflux temperature of the solvent and samples were removed for analysis by syringe. The solvent was removed from the reaction mixture via the vacuum manifold to obtain the products. The imidoyl chlorides exhibited the C=N (neat) stretch near 1670 cm^{-1} in the infrared spectrum.

2-Chloro-*N*,2,2-triphenylacetimidoyl Chloride (3c). Using the above procedure, 271 mg (0.797 mmol) of **2c** was pyrolyzed for 1 h in toluene. The solvent was removed in vacuo and crystallization of the residue from hexane afforded 211 mg (78%) of the crude product, mp 68–71 °C. Recrystallization gave 201 mg (74%) of the pure imidoyl chloride: mp 69.5–71 °C (lit.[10] 67–70 °C); NMR ($CDDl_3$) δ 7.3 (m, aromatic); IR (KBr) 1660 cm^{-1} (C=N).

1-(*N*,2-Diphenyl-2-chloroacetimidoyl)piperidine (4a). Pyrolysis of 0.503 g (0.0019 mol) of **2a** in hot toluene for 24 h followed by a piperidine (2 mL) quench afforded the crude product. The reaction mixture was poured into a 10% potassium hydroxide solution (20 mL) and extracted once with ether (20 mL). The ether extract was dried ($MgSO_4$) and filtered and the solvent removed in vacuo. Chromatography of the residue over alumina (2% EtOAc–hexane) afforded 0.365 g (61%) of the amidine **4a** (via NMR). Crystallization from hexane afforded 0.205 g (34%) of the crystalline amidine: mp 93.5–95 °C; IR (KBr) 1600 cm^{-1} (C=N); NMR (CCl_4) δ 7.4–6.5 (m, 10, aromatic), 6.04 (s, 1, PhCH), 3.3 (m, 4, CH_2N), and 1.4 (m, 6, CH_2).

Anal. Calcd for $C_{19}H_{21}N_2Cl$: C, 72.93; H, 6.78; N, 8.96. Found: C, 72.88; H, 6.69; N, 8.74.

1-[*N*-(1-Naphthyl)-2-chloro-2-phenylacetimidoyl]piperidine (4e). Pyrolysis of **2e** in hot toluene (4 h) with piperidine quench afforded the crude amidine in 63% yield (via NMR) via the above procedure. Crystallization of the amidine from hexane afforded the pure product in 39% yield: mp 106–107.5 °C; IR (KBr) 1600 cm^{-1} (C=N); NMR ($CDCl_3$) δ 8.7–7.2 (m, 12, aromatic), 6.16 (s, 1, PhCH), 3.5 (m, 4, CH_2N), and 1.5 (m, 6, CH_2).

Anal. Calcd for $C_{23}H_{23}N_2Cl$: C, 76.11; H, 6.40; N, 7.72. Found: C, 76.04; H, 6.57; N, 7.40.

Pyrolysis of 2f. Pyrolysis of 0.487 g (0.0015 mol) of **2f** in hot toluene for 4 h followed by a water quench afforded 0.457 g of the crude amides corresponding to the hydrolysis of **5** and **6**. Chromatography of this material over alumina afforded 0.319 g (69%) of the α-chloroamide (via NMR) in the fractions eluted with hexane and 10% EtOAc–hexane. The unsaturated amide, 0.102 g (25%), was obtained in the EtOAc fractions. Crystallization of the appropriate fractions from hexane–EtOAc afforded 0.055 g (14%) of the crude unsaturated amide and 0.172 g (37%) of the crude α-chloroamide. Recrystallization afforded the following analytically pure samples.

***N*-(1-Naphthyl)-2-chloro-2-phenylpropanamide:** mp 131–131.5 °C; IR (KBr) 3300 (N—H) and 1650 cm^{-1} (C=O); NMR (CCl_4) δ 8.2–7.2 (m, 12, aromatic), 8.8 (m, 1, NH), and 2.2 (s, 3, CH_3).

Anal. Calcd for $C_{19}H_{16}ClNO$: C, 73.67; H, 5.21; N, 4.52. Found: C, 73.79; H, 5.21; N, 4.46.

***N*-(1-Naphthyl)-2-phenylpropenamide:** mp 145–146 °C; IR (KBr) 3300 (N—H), 1650 (C=O), and 1600 cm^{-1} (C=C); NMR (CCl_4/$CDCl_3$) δ 8.3–7.2 (m, 13, aromatic and N—H), 5.70 and 6.38 (2, d, CH_2=, J = 1 Hz).

Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.20; H, 5.36; N, 5.01.

Hydrolysis of 2f. The aziridine and water (10 mL) were heated on a steam bath for 15 min and cooled and the mixture was extracted with ether. The ether was dried ($MgSO_4$) and filtered and the solvent was removed in vacuo to afford the NMR sample.

Reaction of 1a with Phenyl(trichloromethyl)mercury. A magnetically stirred solution of 1.0 g (0.00552 mol) of **1a**, 2.41 g (0.00608 mol) of phenyl(trichloromethyl)mercury, and dry benzene (35 mL) was heated at the reflux temperature for 48 h under a nitrogen atmosphere. Filtration of the cooled solution through a medium porous sintered-glass funnel afforded 1.66 g (87%) of phenylmercuric chloride, mp 237–246 °C. The solvent was removed in vacuo to yield a red oil; the NMR spectrum of the oil exhibited a peak at δ 5.8 assigned to **3a** (PhCH). Several drops of water were added to the red oil and the resulting material was chromatographed over alumina. Elution with 2–10% EtOAc–hexane afforded 0.302 g (22%) of the crude amide. Crystallization from ethanol after several treatments with decolorizing carbon afforded 0.286 g (21%) of the amide **10a**, mp 147–150 °C (lit.[20] mp 146–148 °C).

Using the above procedure, 0.183 g (1.01 mmol) of **1a**, 1.58 g (3.99 mmol) of phenyl(trichloromethyl)mercury, and dry benzene (7 mL) afforded 0.167 g (62%) of the crude amide (via NMR) and 0.131 g (53%) of pure amide, mp 148–150 °C.

Preparation of 1-Benzyl-2,2-dichloro-3,3-diphenylaziridine (2d) from Phenyl(trichloromethyl)mercury and Sodium Iodide. To 0.200 g (0.738 mmol) of **1d**, 1.164 g (2.94 mmol) of phenyl(trichloromethyl)mercury, and 0.488 g (2.29 mmol) of sodium iodide in a two-necked flask fitted with condenser, septum, and a maintained nitrogen atmosphere was added freshly distilled DME (7 mL) via syringe. The solution was stirred for 8 h at room temperature. The DME was removed in vacuo, benzene (20 mL) was added, and the mixture was filtered through a sintered-glass funnel to remove the inorganic products (1.274 g). The filtrate was concentrated in vacuo to ~5 mL and filtered to remove the last traces of the inorganic products. Crystallization from hexane–ethyl acetate afforded 0.256 g (98%) of the aziridine, mp 118–134 °C. Recrystallization afforded 0.241 g (92%) of the aziridine, mp 135–137 °C (lit.[1] mp 136–137 °C).

Reaction of 1a with Phenyl(trichloromethyl)mercury and Sodium Iodide. A solution of 133 mg (0.735 mmol) of **1a**, 1.165 g (2.94 mmol) of phenyl(trichloromethyl)mercury, 0.458 (3.06 mmol) of sodium iodide, and dry DME (7 mL) was magnetically stirred under a nitrogen atmosphere for 48 h. Using the above procedure 1.06 g (89%) of phenylmercuric iodide, mp 260–280 °C, was obtained. NMR analysis of the filterate ($CDCl_3$) failed to detected the aziridine; however, the presence of the imidoyl chloride was established. Addition of moist benzene and chromatography of the residue over alumina afforded 115 mg (64%) **10a** via NMR. Crystallization from ethanol afforded 41 mg (23%) of the pure amide, mp 148–150 °C (lit.[20] mp 146–148 °C).

Preparation of 1,3-Diphenyl-2,2-dichloroaziridine (1a) from Phenyl(bromodichloromethyl)mercury. A magnetically stirred solution of 0.424 g (2.34 mmol) of **1a**, 1.283 g (2.91 mmol) of phenyl(bromodichloromethyl)mercury, and dry benzene (5 mL) was heated at the reflux temperature for 2 h under a nitrogen atmosphere. The cooled reaction mixture was filtered to remove the crude phenylmercuric bromide (0.925 g, 89%, mp 274–282 °C). The filtrate was treated with decolorizing carbon and filtered and the solvent was removed in vacuo to afford 0.598 g of a dark oil. This material was triturated with several small portions of chloroform leaving a residue of 0.106 g. The chloroform was removed in vacuo and the residue triturated with 3 × 10 mL portions of hot hexane leaving a residue of 0.125 g. The combined hexane fractions were treated with decolorizing carbon and filtered and crystallization afforded 0.247 g (40%) of the crude aziridine **2a**, mp 87–96 °C. Recrystallization from hexane afforded 0.193 g (31%) of the purified aziridine, mp 98–100 °C (lit.[20] mp 99–100 °C). Several additional recrystallizations were needed to remove the light yellow color from this material.

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Registry No.—**1a**, 538-51-2; **1b**, 14752-72-8; **1c**, 574-45-8; **1d**, 7699-79-8; **1e**, 830-51-7; **1f**, 5307-40-4; **3a**, 10295-39-3; **1c**, 17205-55-9; **4a**, 65016-17-3; **4d**, 65016-18-4; **8**, 622-44-6; **10a**, 5110-77-0; chloroform, 67-66-3; *N*-(1-naphthyl)-2-chloro-2-phenylpropanamide, 65036-36-4; *N*-(1-naphthyl)-2-phenylpropenamide, 65016-19-5; $PhHgCCl_3$, 3294-57-3; PhHgCl, 100-56-1.

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Carbon-13 Nuclear Magnetic Resonance Study of Representative *trans*- and *cis*-1-Alkyl-2-aryl(alkyl)-3-aroylaziridines

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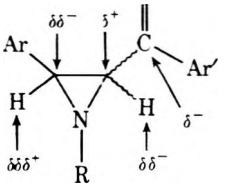
Twenty-two *trans*- and *cis*-1-alkyl-2-aryl(alkyl)-3-aroylaziridines have been studied by use of ^1H and ^{13}C NMR. The ^{13}C chemical shifts of the ring carbons have been tabulated, as well as those for the α-*N*-alkyl carbons (see Table I). Selected coupling constants are reported. The chemical shifts of the ring carbons are correlated with the phenomenon of three-ring to carbonyl hyperconjugation.[2] In addition, the effect of the nitrogen lone pair upon ^1J (^{13}C–H) values and the carbonyl carbon chemical shifts is discussed, while the α-*N*-alkyl carbon values are rationalized in terms of steric compression effects.

A ^{13}C NMR study of representative *trans*- and *cis*-1-alkyl-2-aryl(alkyl)-3-aroylaziridines has been undertaken. While systematic ^{13}C NMR studies of N-unsubstituted alkyl- and phenylaziridines have appeared earlier in the literature,[3,4] no desirable ^{13}C NMR study of the title compounds has been published to date. Work pertaining to the effect of the nitrogen heteroatom in cyclic systems has appeared in the literature,[5–9] as well as that of representative 1-azirines.[10] Here we have studied the effect of three-ring to carbonyl hyperconjugation,[2] the effect of the nitrogen lone pair on selected coupling constants and the carbonyl group, and the steric compression effect (where applicable) in these systems.

The assignments made are based on chemical shift considerations; signal multiplicities from off-resonance decoupling experiments or from coupled spectra; and qualitative considerations of long-range ^{13}C–H couplings; that is to say, the C_2 line width is greater than the line width of C_3 due to three-bond coupling of the C_2 to the adjacent (ortho) protons of the C_2–H aryl substituent (see Table I and the Experimental Section for assignments).

Three-Ring to Carbonyl Hyperconjugation. As revealed in Table I, the ^{13}C NMR studies show that the trans isomers of arylaroylaziridines (except **11a** and **12a**) enjoy substantial conjugation through their three-membered rings. This is borne out by the fact that C_2 appears further downfield than C_3 for **1a**–**8a** and **10a** by 0.5, 1.2, 0.7, 1.3, 1.2, 1.3, 0.9, 0.9, and 1.0 ppm, respectively. The strength of this statement is not so much the ~1-ppm difference in the values of C_3 and C_2 but the fact that the trend is uniform; i.e., $\Delta\delta$ (C_2–C_3) is always greater than zero. (A similar trend is found in the IR and UV data.[2]) In marked contrast, the opposite trend is found in the ^1H NMR data (see again Table I), such that the ring proton attached to C_3 is always further downfield in both the trans and cis isomers. One plausible explanation for this trend in the trans compounds might be the greater anisotropic effect by the phenyl group upon the hydrogen cis to it.[11a–c] Of course,

Chart I. Bond Polarization along the σ Skeleton of Arylaroylaziridines Assuming Carbonyl to be the Only Electronegative Substituent



an alternating polarization effect, such as was invoked in six-membered N-heterocyclic compounds by Morishima,[11c] appears applicable here (Chart I). That is to say, Pople,[11d] using the CNDO–SCF molecular orbital calculations, suggested that the inductive effect induced by an electronegative substituent (here, carbonyl) alternates and attenuates along to σ skeleton of the arylaroylaziridine three ring. This theory appears to be well correlated with the H_2 and H_3 ring proton values in both the *trans*- and *cis*-aziridines (Table I), wherein H_3 ($\delta\delta^-$) is always further downfield than H_2 ($\delta\delta\delta^+$). Moreover, the fact that the ring hydrogens of trans are further downfield than those of the cis can clearly be attributed to the anisotropic effect of the phenyl and carbonyl groups lying cis to their hydrogens in the *trans*-aziridines.[11a] Finally, one cannot ignore the bond polarization effect of the phenyl group since the *trans*- and *cis*-1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)aziridines (**16a,b**) have their C_2 protons significantly upfield, i.e., ~1 ppm, from their respective trans and cis analogues, **11a,b**.[11a,d]

With respect to three-ring to carbonyl hyperconjugation, a brief explanation of the stereochemical requirements is warranted. Basically, following the established corollary[11a,13] that the *N*-alkyl group in the trans series exists preferentially syn to the carbonyl moiety, the following conformer may be drawn to represent **1a**–**8a**, **10a**, and **11a** (see Chart II). In es-

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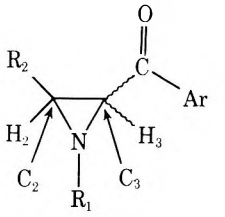
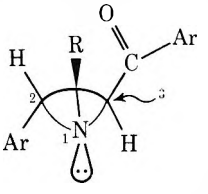
Table I. Proton and Carbon-13 NMR Parameters[d] of Selected *trans*- and *cis*-1-Alkyl-2-aryl(alkyl)-3-aroylaziridines



R_1	R_2	Ar	Trans (cis)	Proton, ppm from Me_4Si[a]			Carbon-13, ppm from Me_4Si			
				H_2	H_3	H_α[b]	C_2	C_3	C_α[b]	Carbonyl C=O
H	Ph	*p*-Ph-C_6H_4	**1a**	3.18	3.55	2.72 (N-H)	43.9	43.4		194.8
Me	Ph	*p*-Ph-C_6H_4	**2a** (**2b**)	3.37 (3.05)	3.55 (3.22)	2.67 (2.60)	49.6 (46.9)	48.4 (49.8)	38.8 (49.8)	193.7 (190.5)
Et	*p*-Ph-C_6H_4	Ph	**3a** (**3b**)	3.52 (3.07)	3.62 (3.23)	2.88 (2.60)	48.7 (49.8)	48.0 (51.2)	45.8 (55.4)	194.2 (193.1)
Bz	Ph	Ph	**4a** (**4b**)	3.62 (3.2)	3.62 (3.32)	4.02 (3.67-3.92)	49.3 (49.6)	48.0 (51.0)	54.8 (63.7)	194.8 (192.8)
i-Pr	*p*-Ph-C_6H_4	Ph	**5a** (**5b**)	3.58 (3.13)	3.67 (3.28)	3.02 (1.85)	48.5 (49.5)	47.3 (50.5)	50.3 (61.6)	194.7 (193.1)
c-C_6H_{11}	Ph	Ph	**6a** (**6b**)	3.57 (3.12)	3.63 (3.28)	2.12 (1-2)	48.4 (49.1)	47.1 (49.8)	57.7 (68.9)	194.5 (193.2)
endo-Norbornyl[c]	Ph	Ph	**7a** (**7b**)	3.50 (3.0)	3.55 (3.07)	3.03 (2.25)	49.0 (49.5)	48.1 (50.6)	60.7 (72.3)	194.6 (193.2)
exo-Norbornyl[c]	Ph	Ph	**8a** (**8b**)	3.35 (3.02)	3.49 (3.06)	2.75 (2.33)	48.3 (49.8)	47.4 (50.5)	64.1 (74.1)	194.6 (193.4)
t-Bu	Ph	Ph	(**9b**)	(3.41)	(3.41)	(-)	(43.2)	(44.3)	(53.7)	(194.0)
c-C_6H_{11}	Ph	*p*-Me-Ph	**10a** (**10b**)	3.57 (3.12)	3.69 (3.28)	2.12 (1-2)	48.1 (49.0)	47.1 (49.8)	57.8 (69.0)	194.0 (192.7)
c-C_6H_{11}	Me	*p*-Ph-C_6H_4	**11a** (**11b**)	2.68 (2.11)	3.32 (2.94)	2.12 (-)	42.1 (42.7)	44.3 (46.5)	58.0 (69.4)	194.9 (194.6)
Me	*p*-NO_2-Ph	Ph	**12a**	3.52	3.60	2.62	48.0	49.3	38.6	193.2
c-C_6H_{11}	H	*p*-Ph-C_6H_4	**13**	2.29	2.93	1.77	35.7	39.8	69.5	195.6

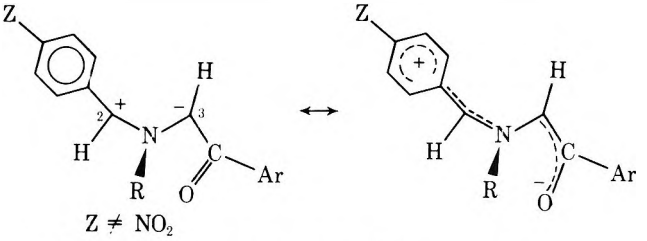
[a] See ref 11a for details on how these compounds were studied by ^1H NMR. [b] The α position refers to either the carbon attached to nitrogen or its hydrogen(s). [c] These newly synthesized[12] isomeric aziridines gave satisfactory microanalysis. [d] Cis values in parentheses.

Chart II. Conformation of Trans Isomers in *N*-Alkylarylaroylaziridines[a]



[a] Ar = Ph or *p*-Ph-C_6H_4; R = H, Me, Et, *i*-Pr, c-C_6H_{11}, etc. (alkyl).

Chart III. Representation of Canonical Structures Which Serve to Resonance Stabilize the C-C Bond Conjugation[a]



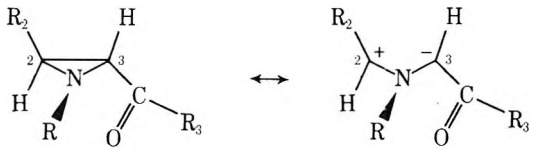
[a] If Z = H, ten structures are possible.

sence the steric requirements demand that the nodal plane of the phenyl and carbonyl groups be orthogonal to the plane of the aziridine ring.[2] Hence, the π orbitals of the attached groups have to be free to orient themselves so that their nodal planes approach a perpendicular relationship to the plane of the three ring and a symmetrical arrangement with respect to the bent bonds.[2,14,15] Furthermore, it appears that the conjugative behavior of the three ring is due to the C–C bond and can well be rationalized by drawing canonical structures of the type shown in Chart III.

It is worth noting that the ability of the aryl ring (attached to C_2) to support a partial positive charge is most crucial. When *trans*-1-methyl-2-(*p*-nitrophenyl)-3-benzoylaziridine (**12a**) was examined by ^{13}C NMR, C_2 was found 1.3 ppm *upfield* from C_3. Another model for comparison in support of three-ring to carbonyl hyperconjugation is to look at the *trans*- and *cis*-methyl 1-isopropyl-2-(*p*-biphenyl)aziridinecarboxylates (**15a,b**) spectroscopically and observe the net change in C_2 and C_3 values in going from trans to cis relative to the ketone analogues **5a,b.**[16a] For the esters the $\delta\Delta\delta$ (C_2–C_3) value was 1.3 ppm vs. a $\delta\Delta\delta$ (C_2–C_3) value of 2.2 ppm for the ketone. As expected, the ketone shows a greater conjugative effect in the trans isomer, owing to its better ability to support a partial negative (δ^-) charge at C_3 (Chart III). The apparent inference from these data is that in **12a** and **15a** the C_2–C_3 bond polarity is significantly diminished (Chart IV)[16b] with a resultant decrease in three-ring to carbonyl hyperconjugation. However, not only must electronic considerations be met, but also steric requirements must be fulfilled in order for three-ring to carbonyl hyperconjugation to occur; here the cis analogues are a prime example of this (see below).

In marked contrast to the trans isomers, the *cis*-1-alkyl-2-aryl-3-aroylaziridines (**2b–10b**) have their C_2 carbons 2.9,

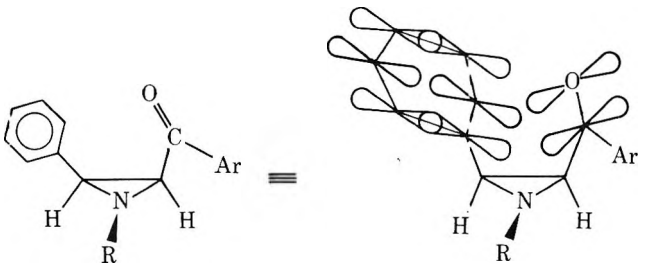
Chart IV. *trans*-Aziridines with Lowered Carbonyl Hyperconjugation



R_1 = *p*-$NO_2C_6H_4$ when R_3 = Ph
R_2 = *p*-PhC_6H_4 when R_3 = OCH_3

relatively minor

Chart V. Gauche Conformer of *cis*-*N*-Alkylarylaroylaziridines



0.4, 1.4, 1.0, 0.7, 1.1, 0.7. 1.1, and 0.8 ppm, respectively, upfield from C_3 (Table I). Again the trend is uniform; however, now $\Delta\delta$ (C_2–C_3) is always less than zero. This trend can be attributed, in part, to diminished three-ring to carbonyl hyperconjugation. Although a cisoid conformer of the cis isomer may be postulated, it is the gauche conformer (Chart V) which has been found to be the main, if not only, conformer present in polar solvent, as revealed by infrared studies,[12,17-19] and it lacks the ability to hyperconjugate. (Note: in the gauche conformer repulsion between the C_2-aryl group and C_3-carbonyl group will not allow for the orbital overlap needed for three-ring to carbonyl hyperconjugation.)

Effect of Nitrogen Lone Pair. An analysis of the chemical shifts of carbonyl carbons in the arylarolyaziridines (Table I) reveals that a consistent, substantial difference exists between the trans and cis isomers. In pairs **2**–**8** signals of the carbonyl carbons are downfield in the trans isomer compared to the cis by 1–4 ppm. In compounds **11a,b**, which lack an aromatic group at C_2, the carbonyl chemical shifts are rather similar, which suggest that an aromatic group at C_2 is a necessary ingredient to observe a substantial effect. The identity of the N–R substituent does not appear to have a sizable effect (compare **2**, **3**, and **6**–**8**), as long as R is attached to the nitrogen with a primary, secondary, or tertiary carbon. The trans isomers **2a**–**8a** appear rather similar to their carbocyclic analogue, *trans*-1-(*p*-phenylbenzoyl)-2-phenylcyclopropane (**14**) (Chart VI), except that **14** has an even more downfield carbonyl chemical shift. This similarity suggests that the orientation of the lone pair is not of major importance. In particular, the *trans*-aziridines, which have the lone pair anti to carbonyl, show downfield carbonyl absorptions, compared to the *cis*-aziridines, where carbonyl is syn to the nitrogen lone pair. The shielded nature of the chemical shifts in the cis isomers is presently believed to be due to anisotropic effect, whereby the circulation of electrons in the π system of one substituent shields the other group, and is the case in the *cis*-aziridines because of the shielding effect of the aromatic group at C_2. (In

Chart VI. Carbocyclic Analogue of *trans*-Arylaroylaziridines

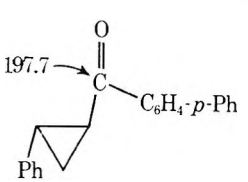
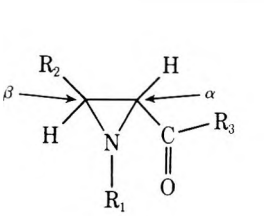
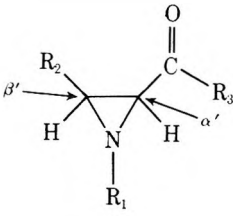


Table II. Stereochemical Dependence of ^{13}C–H Coupling Constants[a] in Selected Aroylaziridines



trans



cis

Compd					
Trans	Cis	J_α	J_β	$J_{\alpha'}$	$J_{\beta'}$
	4b			164	166
5a	**5b**	172	167	162	163
6a	**6b**	177	166	162	164
10a		176	166		
11a		174	164		
12a		171	167		
15a	**15b**	181	167	170	167

[a] *J* values in hertz.

Table III. Calculated vs. Experimental Values[a] for the α-*N*-Alkyl Carbon in *trans*- and *cis*-Arylaroylaziridines

Trans	Cis	N substituent	Exptl	Calcd
2a	2b	-$\overset{*}{C}H_3$	38.8 (49.8)	38.8 (49.2)
3a	3b	-$\overset{*}{C}H_2CH_3$	45.8 (55.4)	45.0 (55.4)
4a	4b	-$\overset{*}{C}H(CH_3)_2$	50.3 (61.6)	51.2 (61.6)
5a	5b	-$\overset{*}{C}H_2Ph$	54.8 (63.7)	52.3 (62.7)
6a	6b		57.7 (68.9)	58.5 (68.9)
7a	7b		60.7 (72.3)	63.2 (73.6)
8a	8b		64.1 (74.1)	63.2 (73.6)

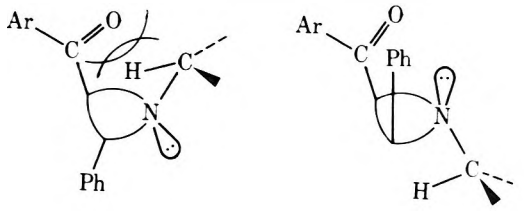
[a] Cis values in parentheses.

^1H NMR, the mutual shielding of aromatic groups near in space is rather common, but in ^{13}C NMR such observations are less frequent.[20-22])

Jennings and co-workers[23] have observed a stereochemical dependence of ^{13}C–H coupling constants in diastereomeric (*Z*)-*cis*- and (*E*)-*trans*-oxaziridines. Similarly, ^1J (^{13}C–H) coupling constants in selected *trans*- and *cis*-*N*-alkylarlaroylaziridines show such a dependence (see Table II) on the orientation of the nitrogen lone pair such that a positive increment is imparted to the coupling constant of nearby ^{13}C–H for a C–H bond cis to the lone pair. For **5a**, **6a**, and **10a**–**12a** (all trans) the difference is in agreement with these findings and the supposition that the preferred conformation is the lone pair syn to phenyl. On the other hand, for **4b**–**6b** (all cis) the ^1J (^{13}C–H) coupling constants are similar, as expected, and this indicates that the nitrogen lone pair is anti in orientation to both ring protons.

Steric Compression Effect. The value of the chemical shifts of the α-*N*-alkyl carbon increases in both the trans and cis isomers as cited in Table III. Hence, a mean difference of 10.4 ppm is found in the chemical shift between the cis and trans isomers, and looking at the conformations of the isomers (Chart VII) one can postulate that the α-*N*-alkyl carbon in the trans isomer is sterically perturbed by being syn to the carbonyl moiety. In the cis isomer no steric compression shift is

Chart VII. Effect of Steric Compression Shift



observed since the α-*N*-alkyl carbon is anti to the benzoyl group. Since, in this steric perturbation, the carbon to hydrogen bond is shortened and the subsequent carbon electron density increases, it is not surprising that the α-*N*-alkyl carbon in the trans isomer is found (on the average) 10.4 ppm upfield from its unperturbed cis analogue. As the magnitude of the shift is quite large, it appears that the proximity of the α-*N*-alkyl hydrogen(s) and the carbonyl group is an important factor in determining the chemical shift of the α carbon attached to nitrogen.[24]

Of importance also is the order in which the chemical shifts of the α-*N*-alkyl carbon increase (goes downfield) relative to Me_4Si. This trend can be attributed to the fact that the presence of attached and nearby carbons has a profound effect upon ^{13}C NMR chemical shifts. In order that a quantitative grasp of the effect of the attached carbons can be understood, one can derive and employ the following empirical equation (1) for the ^{13}C chemical shift for the *N*-alkyl carbon α to nitrogen

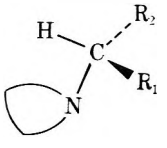
$$\delta^{c}_{calcd} = B c\alpha + \alpha N_1 + \beta N_2 + S \qquad (1)$$

where $Bc\alpha$ is the base value, taken as 49.2 ppm, N_1 = number of α carbons to carbon α to nitrogen, N_2 = number of β carbons to carbon α to nitrogen, α = 6.2, β = 3.65, and S = steric compression factor = −10.4 ppm (trans isomer only). Hence, by employing this equation one can calculate values for non-tertiary α-*N*-alkyl carbons that are quite close to those values found experimentally; in fact, the calculated (δ^{c}_{calcd}) and experimental (δ^{c}_{exptl}) values appear in close agreement (see Figure 1).

With respect to the chemical shifts of the ring carbons, the *N*-alkyl substituent appears to have *little or no effect* on the chemical shift values of the arylaziridine carbons since all appear within a few parts per million of one another (except in **9b** when the *N*-alkyl group is *tert*-butyl; cf. discussion below). Ordinarily, the effect of a substituent γ to the C_2 and C_3 would be substantial, according to Stothers;[21] however, little effect is observed in this instance. One reason may be that the hydrogen of the α-*N*-alkyl carbon is always extending toward the center of the three ring and impinging on the C_2 and C_3 substituents (Chart VIII). This argument is reinforced by the fact that the small C–N–C angle of the aziridine ring makes it difficult to accommodate any other group than hydrogen "inside" the three ring. Thus, it makes little difference what N–CH–R_1R_2 is because R_1 and R_2 are always extended away from the ring. Moreover, when *tert*-butyl is the *N*-alkyl substituent in the case of **9b**, both ring carbons show an upfield shift owing to a probable steric compression effect by a methyl group which must in this instance lie over the three ring.[20,21]

Another steric compression shift may be found in the

Chart VIII. Conformer of Arylaroylaziridine with the Hydrogen of the *N*-Alkyl Carbon Pointing toward the Center of the Aziridine Ring



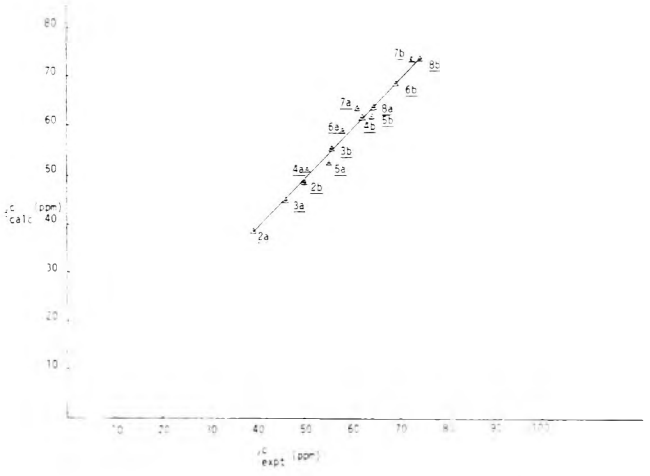


Figure 1. Plot of α-*N*-alkyl carbons [δ^{c}_{calcd} (ppm) vs. δ^{c}_{exptl} (ppm)] with regression analysis used to get the best least-squares correlation of all the points, the best straight line of which is found to be δ^{c}_{calcd} = 1.016, δ^{c}_{exptl} − 1.021, with the correlation coefficient (r^2) = 0.993.[25]

chemical shifts of the C_2-methyl group in **11a** and **11b**. For **11a** δ = 18.7 ppm, while **11b** has a 13.5-ppm shift. This is another case of a steric substituent shift wherein the C_2-methyl group cis to the carbonyl is shifted 5.2 ppm upfield in the cis isomer, a considerably smaller value than what is observed in the case of the α-*N*-alkyl carbon. The reason may be due to the fact that the C–N bond length in aziridine is considerably shorter than the C–C bond length, in this case approximately 0.10 Å shorter.[2,15] This places the substituent on N in closer proximity to a syn group than a substituent on C_2, creating a worse steric situation for the former and, hence, a greater steric shift.

Experimental Section[26]

These epimeric 1-alkyl-2-aryl(alkyl)-3-aroylaziridines were prepared by known procedures: **1a** and **2a**,[27] **3a,b** and **5a,b**,[11a] **4a,b**, **6a,b**, **9b**, **10a,b**, and **12a**,[28] **7a,b** and **8a,b**,[12,28] **11a,b**,[29] **13**,[30] **14**,[31] and **15a,b**.[11a]

The ^1H noise-decoupled and single-frequency off-resonance decoupled ^{13}C Fourier transform NMR spectra were determined from ca. 1 M $CDCl_3$ solutions on a Varian XL-100-15 spectrometer. Digital resolution is 1.25 Hz/point. Chemical shifts are referenced to internal $CDCl_3$, taken as 76.9 ppm from Me_4Si, and are accurate to 0.1 ppm.[32] Listed below is the complete ^{13}C NMR data for the *trans*- and *cis*-arylaroylaziridine systems.

***trans*-2-Phenyl-3-(*p*-phenylbenzoyl)aziridine (1a):** δ 194.8 (s, C=O), 146.3, 138.1, 134.4 (s, aromatic ipso C's), 126.0–129.0 (m, aromatic C–H's), 43.9 (d, C_2), 43.4 (d, C_3).

***trans*-1-Methyl-2-phenyl-3-(*p*-phenylbenzoyl)aziridine (2a):** δ 193.7 (s, C=O), 145.9, 139.6, 139.5 (s, aromatic ipso C's), 125.9–130.1 (m, aromatic C–H's), 49.6 (d, C_2), 48.4 (d, C_3), 38.8 (q, N–CH_3).

***trans*-1-Ethyl-2-(*p*-biphenyl)-3-benzoylaziridine (3a):** δ 194.2 (s, C=O), 140.6, 137.9, 133.1 (s, aromatic ipso C's), 126.9–128.5 (m, aromatic C–H's), 48.7 (d, C_2), 48.0 (d, C_3), 45.8 (t, N–CH_2), 14.8 (q, CH_3).

***trans*-1-Benzyl-2-phenyl-3-benzoylaziridine (4a):** δ 194.8 (s, C=O), 134.6, 132.9, 132.7 (s, aromatic ipso C's), 126.2–128.1 (m, aromatic C–H's), 54.8 (t, N–CH_2), 49.3 (d, C_2), 48.0 (d, C_3).

***trans*-1-Isopropyl-2-(*p*-biphenyl)-3-benzoylaziridine (5a):** δ 194.7 (s, C=O), 140.7, 140.1, 138.0 (s, aromatic ipso C's), 126.2–132.9 (m, aromatic C–H's), 50.3 (d, N–CH), 48.5 (d, C_2), 47.3 (d, C_3), 22.3 (q, CH_3), 22.1 (q, CH_3).

***trans*-1-Cyclohexyl-2-phenyl-3-benzoylaziridine (6a):** δ 194.5 (s, C=O), 139.2, 138.0 (s, aromatic ipso C's), 126.3–133.0 (m, aromatic C–H's), 57.7 (d, N–CH), 48.4 (d, C_2), 47.1 (d, C_3), 33.0 (t, cyclohexyl C_2), 32.7 (t, cyclohexyl C_6), 26.0 (t, cyclohexyl C_4), 24.5 (t, cyclohexyl C_5), 24.2 (t, cyclohexyl C_3).

***trans*-1-(2-*endo*-Norbornyl)-2-phenyl-3-benzoylaziridine (7a):**[33,34] δ 194.6 (s, C=O), 139.5, 138.0 (s, aromatic ipso C's), 126.2–133.0 (m, aromatic C–H's), 60.7 (d, N–C–H or nb C_2), 49.0 (d, C_2), 48.5 (d, nb C_1), 48.1 (d, C_3), 41.0 (t, nb C_3), 38.4 (t, nb C_7), 37.3 (d, nb C_4), 29.8 (t, nb C_5), 22.1 (t, nb C_6).

***trans*-1-(2-*exo*-Norbornyl)-2-phenyl-3-benzoylaziridine (8a):**[33,34] δ 194.6 (s, C=O), 139.4, 137.9 (s, aromatic ipso C's), 125.9–133.0 (m, aromatic C–H's), 64.1 (d, N–CH or nb C_2), 50.2 (d, nb C_1), 48.3 (d, C_2), 47.4 (d, C_3), 42.8 (t, nb C_3), 36.0 (d, nb C_4), 35.8 (t, nb C_7), 28.7 (t, nb C_5), 26.5 (t, nb C_5).

***trans*-1-Cyclohexyl-2-phenyl-3-(*p*-toluyl)aziridine (10a):** δ 194.0 (s, C=O), 143.8, 139.3, 135.6 (s, aromatic ipso C's), 126.3–129.1 (m, aromatic C–H's), 57.8 (d, N–CH), 48.1 (d, C_2), 47.1 (d, C_3), 33.1 (t, cyclohexyl C_2), 32.7 (t, cyclohexyl C_6), 26.0 (t, cyclohexyl C_4), 24.6 (t, cyclohexyl, C_5), 24.2 (t, cyclohexyl, C_3), 21.6 (q, Ar–CH_3).

***trans*-1-Cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)aziridine (11a):** δ 194.9 (s, C=O), 145.5, 139.5, 136.9 (s, aromatic ipso C's), 127.0–128.7 (m, aromatic C–H's), 58.0 (d, N–CH), 44.3 (d, C_3), 42.1 (d, C_2), 33.2 (t, cyclohexyl C_2), 33.0 (t, cyclohexyl C_6), 25.9 (t, cyclohexyl C_4), 24.8 (t, cyclohexyl C_5), 24.4 (t, cyclohexyl C_3), 18.7 (q, CH_3).

***trans*-1-Methyl-2-(*p*-nitrophenyl)-3-benzoylaziridine (12a):** δ 192.3 (s, C=O), 147.1, 146.3, 137.4 (s, aromatic ipso C's), 123.1–133.5 (m, aromatic C–H's), 49.3 (d, C_3), 48.0 (d, C_2), 38.6 (q, N–CH_3).

1-Cyclohexyl-2-(*p*-phenylbenzoyl)aziridine (13): δ 195.6 (s, C=O), 145.5, 139.6, 135.4 (s, aromatic ipso C's), 127.0–128.7 (m, aromatic C–H's), 69.9 (d, N–CH), 39.8 (t, C_2), 35.7 (d, C_3), 32.7 (t, cyclohexyl C_2), 32.3 (t, cyclohexyl C_6), 25.9 (t, cyclohexyl C_4), 24.7 (t, cyclohexyl C_3 and C_5).

***trans*-1-(*p*-Phenylbenzoyl)-2-phenylcyclopropane (14):**[31] δ 197.7 (s, C=O), 145.4, 140.3, 139.7 (s, aromatic ipso C's), 126.1–128.7 (m, aromatic C–H's), 29.8, 29.3 (both d, C_1, C_2, or C_2, C_1), 19.2 (t, C_3).

Methyl *trans*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (15a):[11a] δ 169.2 (s, C=O), 140.6, 140.4 (s, aromatic ipso C's), 126.9–128.5 (m, aromatic C–H's), 51.6 (d, N–CH), 47.6 (d, C_2), 44.1 (d, C_3), 21.8 (q, CH_3), 21.4 (q, CH_3).

***cis*-1-Methyl-2-phenyl-3-(*p*-phenylbenzoyl)aziridine (2b):** δ 190.5 (s, C=O), 146.8, 139.4, 138.1 (s, aromatic ipso C's), 127.2–130.4 (m, aromatic C–H's), 49.8 (q, N–CH_3), 49.8 (d, C_3), 46.9 (d, C_2).

***cis*-1-Ethyl-2-(*p*-biphenyl)-3-benzolaziridine (3b):** δ 193.1 (s, C=O), 140.0, 137.0, 134.3 (s, aromatic ipso C's), 126.6–132.7 (m, aromatic C–H's), 55.4 (t, N–CH_2), 51.2 (d, C_3), 49.8 (d, C_2), 14.1 (q, CH_3).

***cis*-1-Benzyl-2-phenyl-3-benzoylaziridine (4b):** δ 192.8 (s, C=O), 137.6, 136.8, 134.8 (s, aromatic ipso C's), 127.0–132.7 (m, aromatic C–H's), 63.7 (t, N–CH_2), 51.0 (d, C_3), 49.6 (d, C_2).

***cis*-1-Isopropyl-2-(*p*-biphenyl)-3-benzoylaziridine (5b):** δ 193.1 (s, C=O), 134.4–140.6 (s, aromatic ipso C's), 126.4–128.3 (m, aromatic C–H's), 61.6 (d, N–CH), 50.5 (d, C_3), 49.5 (d, C_2), 21.8 (q, CH_3), 21.5 (q, CH_3).

***cis*-1-Cyclohexyl-2-phenyl-3-benzoylaziridine (6b):** δ 193.2 (s, C=O), 137.0, 135.5 (s, aromatic ipso C's), 127.0–135.5 (m, aromatic C–H's), 68.9 (d, N–CH), 49.8 (d, C_3), 49.1 (d, C_2), 32.2 (t, cyclohexyl C_2), 31.8 (t, cyclohexyl C_6), 26.0 (t, cyclohexyl C_4), 24.5 (t, cyclohexyl C_3 and C_5)

***cis*-1-(2-*endo*-Norbornyl)-2-phenyl-3-benzoylaziridine (7b):**[32,33] δ 193.2 (s, C=O). 137.2, 135.3 (s, aromatic ipso C's), 126.9–132.4 (m, aromatic C–H's), 72.3 (d, N–CH or nb C_2), 52.5 (d, nb C_1), 50.6 (d, C_3), 49.5 (d, C_2), 40.9 (t, nb C_5), 38.3 (t, nb C_7), 37.1 (d, nb C_4), 29.8 (t, nb C_5), 22.6 (t, nb C_6).

***cis*-(2-*exo*-Norbornyl)-2-phenyl-3-benzoylaziridine (8b):**[32,33] δ 193.4 (s, C=O), 137.2, 135.5 (s, aromatic ipso C's), 126.9–132.4 (m, aromatic C–H's), 74.1 (d, N–CH or nb C_2), 51.9 (d, nb C_1), 50.5 (d, C_3), 49.8 (d, C_2), 42.2 (t, nb C_3), 35.9 (d, nb C_4), 35.6 (t, nb C_7), 28.9 (t, nb C_5), 26.4 (t, nb C_6).

***cis*-1-*tert*-Butyl-2-phenyl-3-benzoylaziridine (9b):** δ 193.0 (s, C=O), 132.4, 128.3 (s, aromatic ipso C's), 126.9–127.6 (m, aromatic C–H's), 53.7 (s, N–C), 44.2 (d, C_3), 43.2 (d, C_2), 26.5, 26.4, 26.3 (all quartets, CH_3).

***cis*-1-Cyclohexyl-2-phenyl-3-(*p*-toluyl)aziridine (10b):** δ 192.7 (s, C=O), 143.3, 135.7, 134.6 (s, aromatic ipso C's), 126.9–128.8 (m, aromatic C–H's), 69.0 (d, N–CH), 49.8 (d, C_3), 49.0 (d, C_2), 32.3 (t, cyclohexyl C_2), 31.9 (t, cyclohexyl C_6), 26.0 (t, cyclohexyl C_4), 24.5 (t, cyclohexyl C_3 and C_5), 21.6 (q, Ar–CH_3).

***cis*-1-Cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)aziridine (11b):** δ 194.6 (s, C=O), 145.4, 139.6, 136.0 (s, aromatic ipso C's), 127.0–128.7 (m, aromatic C–H's), 69.4 (d, N–CH). 46.5 (d, C_3), 42.7 (d, C_2), 32.8 (t, cyclohexyl C_2), 31.9 (t, cyclohexyl C_6), 25.9 (t, cyclohexyl, C_4), 24.8 (t, cyclohexyl, C_3 and C_5), 13.5 (q, CH_3).

Methyl *cis*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (15b):[11a] δ 168.7 (s, C=O), 140.6, 140.4 (s, aromatic ipso C's), 126.5–128.5 (m, aromatic C–H's), 61.2 (d, N–CH). 47.4 (d, C_2), 45.2 (d, C_3), 21.8 (q, CH_3), 21.4 (q, CH_3).

Acknowledgment. This work was supported in part by Grant CA-02931 from the National Cancer Institute of the U.S. Public Health Service.

Registry No. —**1a,** 40208-64-8; **2a,** 6372-52-7; **2b,** 7570-82-3; **3a,** 32044-34-1; **3b,** 32044-33-0; **4a,** 6476-12-6; **4b,** 6372-57-2; **5a,** 32044-36-3; **5b,** 32044-35-2; **6a,** 2211-61-2; **6b,** 2211-65-6; **7/8,** 64600-17-5; **9b,** 20847-26-1; **10a,** 6372-29-8; **10b,** 6476-39-7; **11a,** 32044-50-1; **11b,** 6372-59-4; **12a,** 64611-65-0; **13,** 6372-55-0; **14,** 64600-18-6; **15a,** 23214-22-4; **15b,** 23214-21-3.

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(12) In the nonpolar solvent, carbon tetrachloride, two carbonyl bands appear corresponding to the gauche and cisoid conformers, while in more polar solvents (chloroform or acetonitrile) only the carbonyl band corresponding to the gauche conformer appears in the cis isomers. For more details, see P. Tarburton, L. J. Wolpa, R. K. Loerch, T. L. Folsom, and N. H. Cromwell, *J. Heterocycl. Chem.*, **14,** 1203 (1977).
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(16) (a) It is a well-known fact that ester carbonyls offer less stabilization to an adjacent (or α) carbanion than ketone carbonyls. (b) Other factors such as excitation energy should also affect the chemical shift; for more details, see J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
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(25) When $r^2 > 0.9$ it is indicative of excellent correlation between two variables; for further details, see C. E. Schwarz, "Used Math", Prentice-Hall, Englewood Cliffs, N.J., 1973, pp 101–106.
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(32) As a check for solvent effects by the $CDCl_3$, selected samples were run with with $CDCl_3$ and Me_4Si; however, the chemical shifts obtained [relative to Me_4Si ($\delta = 0.0$)] were *identical* in all respects with samples run with $CDCl_3$ only.
(33) See ref 20, p 48, for details on how the norbornyl carbons were assigned; for the norbornylaziridines, very close ^{13}C signals were averaged as they were representative of different conformers present in solution.
(34) It is interesting to take note of the fact that when F. M. Menger and T. E.

Thanos, *J. Am. Chem. Soc.*, **98**, 3267 (1976), studied amine quaternization rates in *exo*- and *endo*-2-dimethylaminonorborane, the endo amine quaternized 20 times slower than the exo. However, Menger considered this to be a small factor, which is to say that the *endo*-dimethylamino group is not subjected to unusual steric effects within the endo cavity. The ^{13}C data obtained on **7a,b** and **8a,b** indirectly support Menger's observations because the steric substituent effect, as well as the other chemical shift values for the norbornyl carbons, is about the same in both **7** and **8**. However, a greater "freedom of motion" is observed in the exo case, owing to its greater ability to achieve minimum strain since there is some freedom of motion with respect to the *exo*-norbornyl skeleton. On the other hand, for the endo there is less freedom of motion (its cavity is smaller); hence, the hydrogen on the *endo*-α-*N*-alkyl carbon is more rigidly held in a specific orientation, thereby giving it a larger steric compression shift. Of course, the difference in steric shift of the endo (11.6 ppm) vs. exo (10.0 ppm) is quite moderate.

Synthesis of the 2,3-Dihydro-6*H*-1,4-oxazin-2-ones Chiral at C(3) and Asymmetric Induction in Hydrogenation of the Azomethine Bond

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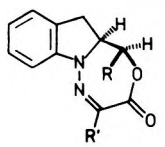
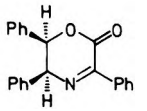
The 2,3-dihydro-6*H*-1,4-oxazin-2-ones **17–26** chiral at C(3) have been prepared, starting from various α-halomethyl aryl ketones and N-protected α-amino acids via intermediary α-(O-α′-N′-protected aminoacyl) hydroxy ketones **1–8** and corresponding hydrobromides **9–16**. 1,3-Asymmetric induction in hydrogeneration of the azomethine bond in **17–24** led to 1,3-disubstituted tetrahydrooxazin-2-ones **27–34**. Their diastereomeric purity was estimated as >98%, based on the analysis of their LIS–NMR spectra, whereas their "3,5-cis" relative configuration was proposed on the grounds of the direction taken by the hydrogenation, based on the conformational analysis of the starting 2,3-dihydro derivatives **17–24**. Heterogeneously catalyzed hydrogenation of the chiral six-membered azomethine derivatives, investigated for the short series of ligands (Me, *i*-Pr, Bz) at the original chiral center, revealed that conformational rigidity around an azomethine bond ensures high diastereoselectivity of the process regardless of the spatial requirements of the larger group on the first center.

Hydrogenation of the azomethine double bond with concurrent asymmetric induction is the most widely used method for preparing chiral compounds with an amino group attached to an asymmetric carbon atom. Knowledge of the greatest significance in this field came mostly from studies by Hiskey and Northrop,[1-3] Harada,[4-6] and Corey.[7,8] Conformational rigidity of the substrate, usually much higher in cyclic than in open-chain azomethine derivatives, significantly enhances the diastereoselectivity of hydrogenation. Thus, reductions of the six- and seven-membered substrates I and II, as carried



I R
a H
b CH_3

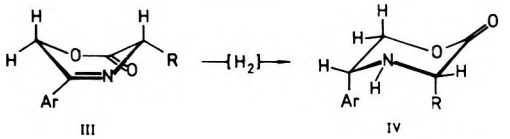


II

out by Corey[6,7] and Kagan,[9] respectively, resulted in nearly 100% stereoselectivity. A recent report[10] of another highly diastereoselective hydrogenation of 2-propyl-5-methyl-$\Delta^{1,2}$-octahydroquinolin in the last step of *d,l*-pumiliotoxin synthesis is also relevant.

Obviously, the high nonequivalence of the diastereotopic faces about the azomethine bond is largely accentuated in cyclic substrates like I and II, which enables a highly stereoselective approach of the reducing agent (diastereoface differentiating reaction[11]). As a part of a wider synthetic program encompassing the preparation of various chiral compounds by diastereoselective azomethine double-bond hydrogenation, we have embarked upon a more detailed study of the diastereoselectivity in 1,3-asymmetric induction obtained with cyclic, six-membered azomethine substrates. Results from this study are the subject of this report.

Scheme I



III IV

Asymmetric hydrogenation of the compounds characterized by the general formulas III, i.e., derivatives of 2,3-dihydro-6*H*-1,4-oxazin-2-ones, has been chosen as an appropriate model reaction (Scheme I).

The envisaged route leading to the azomethine substrates III is shown in Scheme II.

It consists of three steps and starts from easily available prochiral compounds, α-halomethyl ketones, and their equally available chiral counterparts, α-amino acids. This route should lead to C(3)-chiral derivatives III possessing various groups at the inducing chiral center. This, in turn, should allow a study on the dependence of the diastereoselectivity of hydrogenation on the steric requirements of the larger groups R′ on the C(3) atom.

Results and Discussion

To start the synthesis of III according to Scheme II, α-halomethyl ketones and potassium salts of N-protected α-

Scheme II

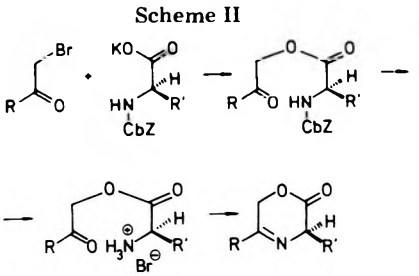


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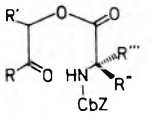
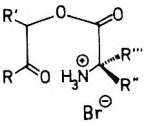
Table I. Esters Prepared from α-Halomethyl Ketones and *N*-Protected α-Amino Acids



Registry no.	Compd	R	R′	R″	R‴	Recrystn solvent	Mp, °C	Yield,[a] %	Analyzed for[b]
6479-48-7	1[c]	Ph	H	H	*i*-Pr	Cyclohexane	103–104	79.5	$C_{21}H_{23}NO_5$
6599-38-3	2	Ph	H	H	Bz	MeOH	92–94	74.0	$C_{25}H_{23}NO_5$
64975-99-1	3	*p*-FPh	H	H	*i*-Pr	Cyclohexane	78–80	74.5	$C_{21}H_{22}FNO_5$
64976-00-7	4	2,5-Di-OMePh	H	H	*i*-Pr	96% EtOH	99–102	100	$C_{23}H_{27}NO_7$
64976-01-8	5	*p*-Biphenylyl	H	H	*i*-Pr	EtOH	107–108	76.8	$C_{27}H_{27}NO_5$
64976-02-9	6	*p*-Biphenylyl	H	H	Me	EtOAc	181–183	87.0	$C_{25}H_{23}NO_5$
64976-03-0	7	*p*-Biphenylyl	H	H	Bz	*i*-PrOH	142–144	84.0	$C_{31}H_{27}NO_5$
64976-04-1	8	2′-Naphthyl	H	H	*i*-Pr	MeOH	98–99	78.9	$C_{25}H_{25}NO_5$

[a] Yields relate to the recrystallized substances. [b] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds listed in the table. [c] N Protected with a *tert*-butoxy group (Boc.)

Table II. Preparation and Physical Properties of Various α-(*O*-Aminoacyl) Hydroxy Ketone Hydrobromides



Registry no.	Compd	R	R′	R″	R‴	Recrystn solvent	Mp, °C	Yield,[a] %	Analyzed for[b]	$[\alpha]_D$	c (in MeOH)
6479-54-5	9	Ph	H	H	*i*-Pr	*i*-PrOH	182–184	95.9	$C_{13}H_{18}BrNO_3$	+12.5°	2.00
6479-55-6	10	Ph	H	H	Bz	Acetone–ether	159–162	90.0	$C_{17}H_{18}BrNO_3$	+5.3°	1.42
64976-05-2	11	p-FPh	H	H	*i*-Pr	*i*-PrOH	160–161	81.3	$C_{13}H_{17}BrFNO_3$	+11.5°	2.06
64976-06-3	12	2,5-Di-OMePh	H	H	*i*-Pr	*i*-PrOH	161–163	82.0	$C_{15}H_{22}BrNO_5$	+12.5°	2.07
64976-07-4	13	*p*-Biphenylyl	H	H	*i*-Pr	MeOH	208–210	97.3	$C_{19}H_{22}BrNO_3$	−6.5°	1.02[c]
64976-08-5	14	*p*-Biphenylyl	H	H	Me	MeOH	217–219	89.0	$C_{17}H_{18}BrNO_3$	−10.3°	1.50[c]
64976-09-6	15	*p*-Biphenylyl	H	H	Bz	MeOH–ether (1:1)	172–174	80.1	$C_{23}H_{22}BrNO_3$	+2.0°	1.15
64976-10-9	16	2′-Naphthyl	H	H	*i*-Pr	EtOH	188–190	98.9	$C_{17}H_{20}BrNO_3$	+20.8°	2.02

[a] Yields are given for crude products. [b] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds listed in the table. [c] Determined in dimethylformamide.

amino acids were condensed in solution at room temperature. DMF was the most favorable solvent. Intermediate esters **1–8** (Table I) have been isolated in yields usually above 90%. (See, however, paragraph concerning supplementary material at the end of the paper.) The Cbz-protecting group was cleaved using 33% hydrobromic acid in acetic acid, as attempted hydrogenolytic cleavage of **1** (10% Pd/C in acetone–MeOH, 1:1, bubbling hydrogen) led, within a few minutes, to hydrogenolysis of the ester group. One of the products was acetophenone in nearly quantitative yield.

The hydrobromides **9–16**, obtained from **1–8**, were isolated in 80–100% yields. Melting points, specific rotations, and other pertinent data of these compounds are summarized in Table II.

A number of trials was necessary to get acceptable yields of the oxazinones **17–24** in the cyclization step. The use of basic or acidic conditions, or of some organic solvents, led to extensive hydrolysis, whereby α-hydroxyl ketones were formed, and concomitant precipitation of the free α-amino acids occurred. Careful reaction control revealed that, on dissolution in water or methanol, the cyclization of some hydrobromides proceeded, indeed, in a clean fashion but was followed by a pH drop from 5 to about 2. This low pH caused extensive hydrolysis and slowed down the cyclization. Therefore, cyclization in acetate buffer at pH 5.0, at room temperature, led clearly to the formation of compounds **17–24** in 65–90% yields (Table III).[12]

On the basis of analysis of Dreiding models for compounds **17–24** conformational equilibria, according to Scheme III, may be proposed.

Two quasi-boat conformations should correspond to the discrete energy minima. In these conformations the bulky R group should markedly inhibit the approach of the reducing agent toward the "α face" of these molecules. This inhibition occurs because of the conically symmetric free-rotation space around the axis of local symmetry of the isopropyl, benzyl, and methyl groups in these compounds. Consequently, coplanar approach toward the "β face", i.e., from above in Scheme III, should be encouraged and a proton on the new chiral center at C(5) should be "1,3-cis" with respect to protons on the C(3) center.[13]

Hydrogenation of dihydrooxazinones was preferably performed by passing hydrogen through methanolic solutions and using 10% Pd/C as a catalyst. Some data characteristic of the compounds **27–34** are given in Table IV. Conditions and reagents used in other attempts at hydrogenation are briefly described in the Experimental Section.

Crude hydrogenation products **27–34** were purified by rapid filtration through silica gel to avoid their decomposition and to retain the original diastereomeric ratio. These samples, and those obtained by recrystallization to a constant rotation value

Scheme III

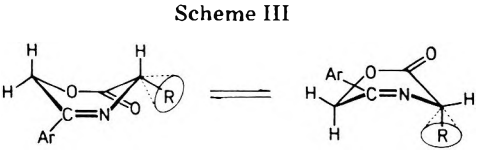
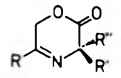


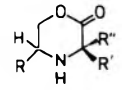
Table III. Preparation and Physical Properties of 2,3-Dihydro-6*H*-1,4-oxazin-2-ones 17–26



Registry no.	Compd	R	R′	R″	Recrystn solvent	Mp, °C	Yield, %	$[\alpha]_D/c$ ($CHCl_3$)	Analyzed for[a]	NMR (in $CDCl_3$)	IR, cm^{-1}
64976-11-0	17	Ph	H	*i*-Pr	Light petroleum	72–74	67.8	−51.6°/5.00	$C_{13}H_{15}NO_2$	1.07 (dd, 6 H), 2.50 (m, 1 H), 3.99 (m, 1 H), 5.23 (ds, 2 H), 7.3–7.8 (m, 5 H)	1738, 1655, 1390, 1370, 690
65085-99-6	18	Ph	H	Bz	MeOH–H_2O (3:1)[2]	58–60	66.2	+26.0°/2.00	$C_{17}H_{15}NO_2$	3.37 (d, 2 H), 4.0–5.15 (m, 2 + 1 H), 7.15–7.55 (m, 10 H)	1755, 1650, 1595, 700
64976-12-1	19	*p*-FPh	H	*i*-Pr	Cyclohexane	75–76	71.1	−45.8°/2.08	$C_{13}H_{14}FNO_2$	1.05 (dd, 6 H), 2.50 (m, 1 H), 4.13 (m, 1 H), 5.29 (ds, 2 H), 7.10 (dd, 2 H), 7.78 (dd, 2 H)	1745, 1665, 1610, 1520, 850
64976-13-2	20	2,5-di-OMePh	H	*i*-Pr	MeOH–H_2O (1:1)[2]	95–97	81.4	−113.2°/ 2.43	$C_{15}H_{19}NO_4$	1.12 (dd, 6 H), 2.50 (ds, 2 H), 3.7 and 3.8 (ss, 2 + 3 H), 4.10 (m, 1 H), 5.22 (ds, 2 H), 6.87 (d, 2 H), 7.21 (d, 1 H)	1752, 1622, 1608, 1500, 826
64976-14-3	21	p-Biphenylyl	H	*i*-Pr	*i*-PrOH	130–132	83.0	−14.6°/1.97	$C_{19}H_{19}NO_2$	1.03 (dd, 6 H), 2.47 (m, 1 H), 4.15 (m, 1 H), 5.30 (ds, 2 H), 7.28–7.9 (m, 9 H)	1740, 1625, 1605, 765, 690
64976-15-4	22	p-Biphenylyl	H	Me			72.3	+20.5°/1.87	$C_{17}H_{15}NO_2$	1.69 (d, 3 H), 4.30 (q, 1 H), 3.32 (m, 2 H), 7.3–8.1 (m, 9 H)	1760, 1630, 1605, 1485, 840, 830, 725, 690
64976-16-5	23	p-Biphenylyl	H	Bz	96% EtOH	160–162	92.5	+273.7°/ 1.37	$C_{23}H_{19}NO_2$	3.38 (d, 2 H), 4.30 (m, 1 H), 4.85 (s, 2 H), 7.2–7.7 (m, 14 H)	1740, 1630, 1605, 760, 698
64976-17-6	24	2′-Naphthyl	H	*i*-Pr	MeOH	91–92	88.2	−49.5°/2.06	$C_{17}H_{17}NO_2$	1.10 (dd, 6 H), 2.57 (m, 1 H), 4.20 (m, 1 H), 5.39 (m, 2 H), 7.4–8.05 (m, 7 H)	1735, 1645, 825, 740
64976-18-7	25	Ph	Ph	H	96% EtOH	116–118	88.4	−9.0°/1.12	$C_{16}H_{13}NO_2$	5.37 (s, 2 H), 5.63 (s, 1 H), 7.3–8.1 (m, 10 H)	1735, ($\nu_{C=O}$), 1655, ($\nu_{C=N}$), 1600, 1580, 1499, 698
64975-85-5	26	*p*-BrPh	Ph	H	Cyclohexane	122–124	89.1	−0.4°/2.64	$C_{16}H_{12}BrNO_2$	5.32 (ds, 2 H), 5.62 (d, 1 H), 7.3–7.9 (m, 9 H)	1745, 1658, 1589, 826

[a] Satisfactory analytical data (±0.3% for C, H, N) were obtained for compounds listed in the table.

Table IV. Preparation and Physical Properties of Tetrahydro-1,4-oxazin-2-ones 27–34



Registry no.	Compd	R	R′	R″	Recrystn solvent	Mp, °C	Yield,[a] %	$[\alpha]_D/c$ ($CHCl_3$) Chromatographed	$[\alpha]_D/c$ ($CHCl_3$) Recrystallized	Analyzed for[b]	NMR (in $CDCl_3$)	IR, cm^{-1}
64975-86-6	**27**	Ph	H	*i*-Pr	MeOH	68–70	61.4	−75.3°/ 2.02[c]	−75.3°/ 2.02[c]	$C_{13}H_{17}NO_2$	1.02 and 1.06 (dd, 6 H), 1.84 (br s, 1 H), 2.4 (m, 1 H), 3.03 (d, 1 H), 4.15 (s, 2 + 1 H), 7.2–7.55 (m, 5 H)	3340 (δ_{NH}), 1730 ($\nu_{C=O}$), 1385, 1370 (*gem*-dimethyl), 710, 700
64975-87-7	**28**	Ph	H	Bz	*n*-Hexane	76–78	45.0	−157.9°/ 2.09	−169.0°/ 2.28	$C_{17}H_{17}NO_2$	2.83 (br s, 1 H), 2.75, 4.35 (m, 6 H), 7.25–7.45 (m, 10 H)	3325 (δ_{NH}), 1730 ($\nu_{C=O}$), 1605 ($\nu_{C=C}$), 700
64975-88-8	**29**	*p*-FPh	H	*i*-Pr		Oil	34.7	−65.0°/ 1.56[c]		$C_{13}H_{16}FNO_2$	1.05 and 1.09 (dd, 6 H), 1.92 (br s, 1 H), 2.4 (m, 1 H), 3.75 (d, 1 H), 4.20 (s, 2 + 1 H), 6.9–7.55 (m, 4 H)	(neat) 3350 (δ_{NH}), 1740 ($\nu_{C=O}$), 1380 (*gem*-dimethyl), 840
64975-89-9	**30**	2,5-di-OMePh	H	*i*-Pr	MeOH	125–126	45.0	−75.5°/ 1.50[c]	−76.3°/ 1.51[c]	$C_{15}H_{21}NO_4$	1.06 and 1.08 (dd, 6 H), 1.80 (br, s, 1 H), 2.5 (m, 1 H), 3.78 and 3.80 (ds, 6 H), 4.05–4.75 (m, 1 + 1 + 2 H), 6.80 (d, 2 H), 7.10 (m, 1 H)	3340 (δ_{NH}), 298–2850 (ν_{CH_3}), 1735 ($\nu_{C=O}$), 1605, 1500, 860, 820
64975-90-2	**31**	*p*-Biphenylyl	H	*i*-Pr	MeOH	142–143	68.9	−83.9°/ 1.65	−84.3°/ 1.90	$C_{19}H_{21}NO_2$	1.05 and 1.10 (dd, 6 H), 2.00 (brs, 1 H), 2.45 (m, 1 H), 3.77 (d, 1 H), 4.22 (s, 2 + 1 H), 7.25–7.7 (m, 9 H)	3350 (δ_{NH}), 1740 ($\nu_{C=O}$), 845, 765, 700
64975-91-3	**32**	*p*-Biphenylyl	H	Me	96% EtOH	164–166	30.6	−56.0°/ 1.39	−81.1°/ 2.00	$C_{17}H_{17}NO_2$	1.52 (d, 3 H), 1.92 (br s, 1 H), 3.88 (q, 1 H), 4.30 (s, 2 + 1 H), 7.2–7.7 (m, 9 H)	3300 (δ_{NH}), 1740 ($\nu_{C=O}$), 1600, 1490, 853, 730, 690
64975-92-4	**33**	*p*-Biphenylyl	H	Bz	96% EtOH	158–160	80.1	−173.8°/ 1.11	−187.7°/ 1.06	$C_{23}H_{21}NO_2$	1.82 (br s, 1 H), 2.75–4.30 (m, 6 H), 7.2–7.7 (m, 14 H)	3320 (δ_{NH}), 1730 ($\nu_{C=O}$), 1600, 760, 700
64975-93-5	**34**	2′-Naphthyl	H	*i*-Pr	MeOH	78–80	50.6	−91.0°/ 1.18	−109.6°/ 1.25	$C_{17}H_{19}NO_2$	1.03 and 1.06 (dd, 6 H), 1.89 (br s, 1 H), 2.45 (m, 1 H), 3.83 (d, 1 H), 4.31 (m, 2 + 1 H), 7.35–7.95 (m, 7 H)	33300 (δ_{NH}), 1730 ($\nu_{C=O}$), 1365, 1368 (*gem*-dimethyl), 1605, 825, 740, 695

[a] Yields are given for chromatographically pure products. [b] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds listed in the table. [c] Determined in methanol.

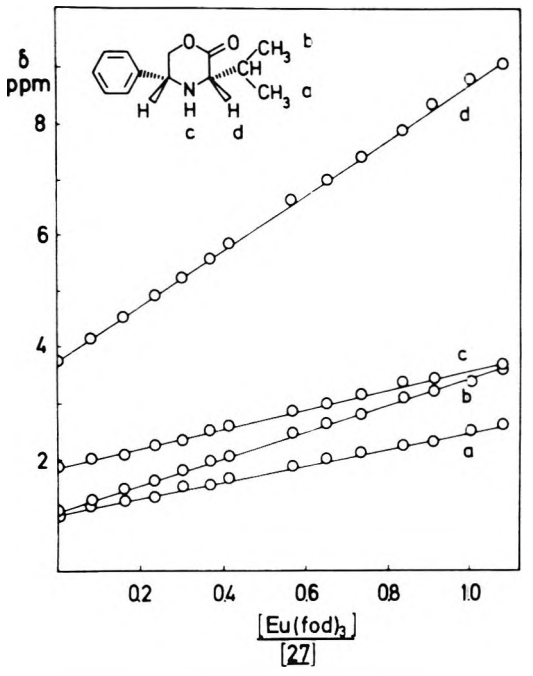


Figure 1. Dependence of the LSR incuced shifts on the reagent/substrate ratio for various groups of protons in compound **27**.

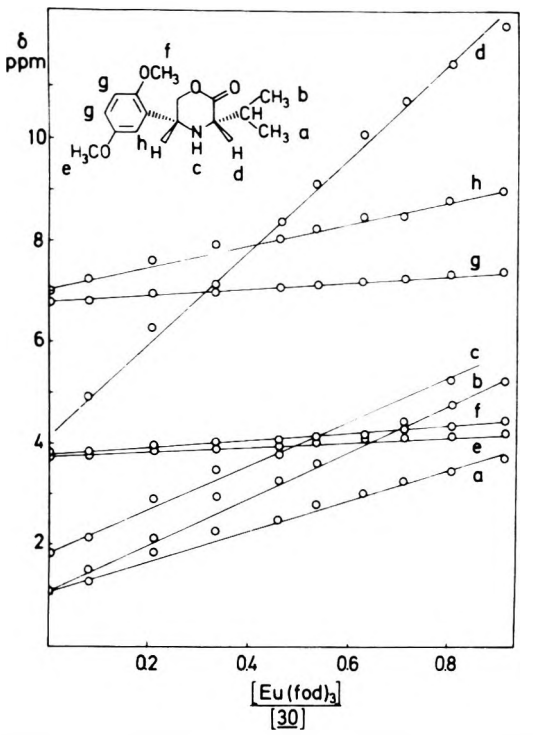


Figure 2. Dependence of the LSR induced shifts on the reagent/substrate ratio for various groups of protons in compound **30.**

(only one recrystallization was usually required), were carefully checked for diastereomeric composition using the LIS method.[14,15] Generally, only one diastereomer was detected using $Eu(fod)_3$ as an achiral reagent. In some cases, signals due to traces of the other diastereomer could be distinguished from the noise of the baseline, but integration of such signals was not possible. We concluded, therefore, that in all cases investigated asymmetric induction led to at least a 98–99% excess of one diastereomer, regardless of the group present on the C(3) chiral center.

Two typical examples of the plot of δ_{meas} vs. lanthanide/substrate concentration ratio for the compounds **27** and **30** are given in Figures 1 and 2.

In all compounds investigated, the proton on C(3) and a proton of the two methyl groups turned out to be the nuclei most sensitive to the addition of LSR. This indicated that the coordination center for the shift reagent is probably the carbonyl oxygen of the lactone group but not the most basic center, i.e., the N(4) atom. Coordination of the lanthanide reagent to the weaker electron-donating center is caused entirely by steric conditions. Two bulky groups (Ar and R) flank the N(4) atom so that an approach of the lanthanide reagent is precluded.

Such selective coordination of the polyfunctional organic molecules, favoring a less nucleophilic center because of the sterical hindrances at the stronger one, was repeatedly observed.[16,17]

In conclusion, it may be stated that high diastereoselectivity of heterogeneously catalyzed hydrogenation of the azomethine double bond, as in compounds **17–24**, was achieved. In these substrates, substituents of different bulkiness were present at the chiral center C(3) (methyl, benzyl, isopropyl). The diastereoselectivity achieved in hydrogenation indicates that in order to obtain high asymmetric induction it is of prime importance to ensure conformational rigidity of the substrate. A substanital difference in the spatial requirements of the ligands on the inducing chiral center is less important.

Experimental Section

Melting points were determined on a Mettler 51 melting point apparatus. Infrared spectra were recorded on Perkin-Elmer M-257 and M-720 spectrometers and are for KBr pellets, unless stated otherwise. A Perkin-Elmer R 12 spectrometer was used to obtain ^1H NMR spectra. All ligand-induced shift (LIS) measurements were performed in $CDCl_3$ solution using Merck $Eu(fod)_3$ Uvasol grade without further purification. Usually, the investigated range of LSR/substrate concentration ratios was from 0.05 to 0.5. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Thin-layer chromatography (TLC) was performed on aluminum or glass plates precoated with Merck's silica gel 60F 254. Column chromatography was run over granular silica gel, 0.05–0.2 mm (Merck).

General Procedure for Preparation of Esters 1–8. N-Protected α-amino acid (50.0 mmol) was dissolved in methanol (50.0 mL), and a solution of potassium hydroxide (2.80 g, 50.0 mmol) in methanol (50.0 mL) was added. Then the solvent was evaporated in vacuo, and the residual potassium salt was dissolved in dimethylformamide (100 mL). To this solution the desired α-halomethyl aryl (or alkyl) ketone (50 mmol) was added, and the reaction mixture was stirred at room temperature. The reaction was followed up by TLC using chloroform–ether (9:1) as the eluant and was usually found to be completed within 20 h. After completion, the dimethylformamide was evaporated in vacuo at 80 °C, the residue was slurried in water (100 mL), and undissolved crude esters were collected by suction, washed with water, and recrystallized from the solvents stated in Table I. The spectroscopic properties are briefly listed below.

Infrared spectra of all compounds exhibited the following characteristic bands (cm^{-1}): 3340–3370 (δ_{NH}), 1740–1755 ($\nu_{COCH_2OC=O}$), 1695–1710 ($\nu_{PHC=O}$), 1680–1690 ($\nu_{HNC=O}$), 1510–1540 (ν_{NH}).

NMR spectra of all compounds (except **2**) exhibited singlets at 5.05–5.15 ppm (2 H) for benzylic protons within the N-Cbz group. All compounds exhibited double singlets between 5.20 and 5.60 ppm (which sometimes collapsed into one singlet) for geminal protons $COCH_2O$. All spectra were recorded in $CDCl_3$ except those for **1**, which were recorded in acetone-d_6.

General Procedure for the Preparation of Compounds 9–16. Compounds **1–8** (30 mmol) were dissolved in 33% hydrogen bromide in acetic acid (100 mL) and stirred until evolution of the gas ceased (0.5–1 h). The resulting solution was diluted by the addition of ether (200 mL), and light petroleum (100 mL) was added to precipitate products. The pasty (sometimes oily) products were brought to crystallization by extended scratching. Crude hydrobromides were collected by suction, washed with ether, and recrystallized from the solvents specified in Table II.

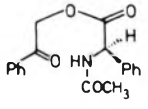
Infrared spectra of all compounds exhibited the following characteristic bands (cm^{-1}): 3000–3100, 2500–2800, 1900–2100 ($-NH_3^+$), 1740–1765 ($\nu_{COCH_2C=O}$), and a $PhC{=}O$ band between 1690 and 1705 cm^{-1}.

NMR spectra were generally recorded in MeOH-d_4, but those of compounds **9** and **13** were recorded in D_2O and those of **13** and **14** in

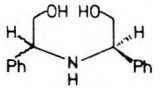
Me_2SO-d_6. The *S*-alanyl derivative **14** exhibited a characteristic doublet-quartet pattern ($CH_3CHCNCO$) centered between 1.60 and 1.73 ppm, and 4.2 and 4.38 ppm, respectively. The *S*-phenylalanyl derivatives **10** and **15** exhibited a simple pattern consisting of a doublet at 3.45 ppm (1 H) and a multiplet centered at 4.5 ppm (2 H). The *S*-valyl derivatives **9, 11, 12,** and **13** exhibited a characteristic doublet due to protons from the two superimposed diastereotopic methylenic groups, at 1.15–1.22 ppm (6 H), and a multiplet for the $(CH_3)_2CH$ proton at 2.30–2.50 ppm.

General Procedure for the Preparation of 3,5-Disubstituted 2,3-Dihydro-6*H*-1,4-oxazin-2-ones 17–26. The hydrobromides **9–16** (10 mmol) were dissolved in 0.2 M acetate buffer (100 mL, prepared from 70 parts of 0.2 M aqueous sodium acetate and 30 parts of 0.2 M acetic acid). The resulting solution was stirred for periods ranging from 2 to 24 h at room temperature, and completeness of the reaction was checked by TLC using chloroform–ether (9:1) or ether–acetone (3:1) as eluting systems. During the reaction, cyclic products precipitated and were separated by suction. Only compound **24** was cyclized for 48 h and, since it did not separate within this period, it was isolated by extraction of the aqueous buffer solution with chloroform (3 × 30 mL). Extracts were combined, dried (Na_2SO_4), and concentrated for crystallization. After recrystallization from the solvents listed in Table III, pure compounds **17–26** were obtained. Their spectroscopic and other characteristic data are given in Table III.

Attempts at Hydrogenation of the C=N Bond in the 2,3-Dihydro-6*H*-1,4-oxazin-2-ones. Various reducing agents or hydrogenation catalysts, or both, were tried to find optimum conditions for the hydrogenation of the C=N bond in compounds **17–26**, e.g., sodium borohydride, diborane, Raney Ni, Pd/$BaSO_4$, and Pd/C (5 and 10%, respectively, from Fluka). The following solvents were used: dioxane, ethyl acetate, acetic anhydride, and methanol. Catalytic hydrogenation by a flow of hydrogen gave rise to a much less hydrogenolytic decomposition than a batch system under otherwise identical reaction conditions (10% Pd/C, methanol). Catalytic hydrogenation proved to be of no use with the C(3) phenyl derivatives **25** and **26**, however, since concomitant hydrogenolysis was inevitable. An attempt to quench the reduced product as the *N*-acetyl derivative, starting from 503 mg (2 mmol) of **25** and using acetic anhydride as the solvent (10.0 mL) and 10% Pd/C catalyst (100 mg), led to compound **35** (508 mg, 81.7%).



35



36

***α*-(*R*)-*N*-Acetylphenylglycyloxyacetophenone (35):** Recrystallized from CCl_4; mp 131–133°C; NMR ($CDCl_3$) δ 1.93 (s, 3 H), 5.26 (s, 2 H), 5.75 (d, 1 H, degenerated into a singlet on addition of D_2O), 6.67 (d, 1 H, disappeared on addition of D_2O), 7.2–7.9 (m, 10 H); IR 3325 (δ_{NH}), 1748 (ν_{CO}, ester), 1715 (ν_{CO}, ketone), 1650 (ν_{CO}, amine), 1551, 698, 690 cm^{-1}; $[\alpha]^{24}D$ +1.0° (c 2.02 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{17}NO_4$ (311.34): C, 69.44; H, 5.50; N, 4.50. Found: C, 69.67; H, 5.30; N, 4.64.

When $NaBH_4$ was used to reduce **25** and **26**, extensive hydrolytic decomposition took place, whereas the use of diborane led to nonselective reduction of both functionalities in **25** to give the diol **36**.

1,1′-Diphenyldiethanolamine (36). The solution of freshly recrystallized sodium brohydride (182 mg, 4.8 mmol) in diglyme (6.0 mL, carefully dried over CaH_2, and freshly distilled from $LiAlH_4$) was added dropwise, during 1 h, to the solution of BF_3·Et_2O (1.2 mL, 9.6 mmol, freshly distilled from CaH_2) in dry diglyme (2.0 mL). Using an apparatus similar to the one described in the literature,[18] a stream of nitrogen was introduced, which carried diborane into a flask containing dihydrooxazin-2-one, **25** (503 mg, 2.0 mmol) dissolved in THF (5.0 mL, dried by a 3-Å molecular sieve). After stirring for 1 h at room temperature, the reaction mixture was heated for another hour at 70–80 °C. Then it was cooled and water (2 mL) and acetic acid (0.5 mL) were added. After subsequent dilution with more water(20 mL), the mixture was extracted with ether (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The oily residue was purified on a column [15 g of silica gel, ether–light petroleum (1:1) as the eluant] to give 248 mg (49%) of oily **36**, which decomposed on attempted metal-block distillation. A pure sample was obtained by repeated chromatography and was dried for 24 h at 0.01 mmHg over P_2O_5: NMR ($CDCl_3$) δ 2.77 (s, 2 H, disappeared on addition of D_2O), 3.70 (m, 2 H), 4.33 (s, 4 H), 4.5–4.8 (m, 2 H), 7.2–7.5 (m, 10 H).

Anal. Calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 5.74; N, 5.44. Found: C, 74.39; H, 6.02; N, 5.33.

General Procedure for the Catalytic Hydrogenation of Compounds 17–24. All compounds (5.0 mmol) were dissolved in methanol (50.0 mL), to which ethyl acetate was sometimes added in order to improve the solubility. Subsequentialy, 100–150 mg of 10% Pd/C was added and the reaction mixture was vigorously stirred while hydrogen was very slowly bubbled through the suspension. The hydrogenation was followed up by TLC using ether–light petroleum (1:1) as the eluant. The reduced products **27–34** appeared as new spots having somewhat smaller R_f values, but exhibiting a much weaker fluorescence under the UV-254 lamp, so that their location with iodine vapors was sometimes required. Reactions were usually completed within 1–3 h, after which the catalyst was filtered off, the filtrate was evaporated, and the crude products were purified, first by chromatography [25 g of silica gel, ether–light petroleum (1:1) as the eluant] and then by crystallization from the solvents listed in Table IV.

Both the chromatographically purified samples of compounds **27–34** and those recrystallized to constant rotations and melting points (usually two crystallizations were sufficient) were analyzed for diastereomeric composition using the LIS method in NMR, as described in the introductory section of this paper.

Note Added in Proof. After this manuscript was accepted for publication, a paper appeared [G. Schulz and W. Steglich, *Chem. Ber.*, **110**, 3615 (1977)] where some of the title compounds were described. The authors explained the reactivity of C(5)-alkyl-1,4-oxazin-2-ones as well.

Registry No.—**35,** 6495-94-6; **36,** 64975-95-7; *N*-Cbz-*S*-Val, 1149-26-4; *N*-Cbz-*S*-Phe, 1161-13-3; *N*-Cbz-*S*-Ala, 1142-20-7; $PhCOCH_2Br$, 70-11-1; *p*-$FC_6H_4COCH_2Br$, 403-29-2; 2,5-di-MeO-$C_6H_3COCH_2Br$, 1204-21-3; *p*-$PhC_6H_4COCH_2Br$, 135-73-9; 2-bromo-1-(2-naphthalenyl)ethanone, 613-54-7; $PhCOCH_2O$-$COCH(Ph)NH_2$·HBr, 64975-77-5; $PhCOCH_2OCOCH(Ph)NH$-Cbz, 64975-96-8; $HO_2CCH(Ph)NH$-Cbz, 17609-52-8; *p*-BrC_6H_4CO-$CH_2OCOCH(Ph)NH_2$·HBr, 64975-79-7; *p*-$BrC_6H_4COCH_2O$-$COCH(Ph)NH$-Cbz, 64975-97-9; *p*-$BrC_6H_4COCH_2Br$, 99-73-0.

Supplementary Material Available. Full spectroscopic (IR, NMR) and analytical data for other intermediary compounds prepared during this work (5 pages). Ordering information is given on any current masthead page.

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(12) Note: All compounds in Table III possess a C(5)-aryl group, but no dihydrooxazin-2-one derivatives bearing a C(5)-alkyl group could be isolated from corresponding reaction mixtures. (See paragraph on supplementary material at the end of the paper). Attempts to bring about cyclizations of such compounds failed, even when weak ion-exchange resins or 3-Å molecular sieves were used as cyclization promotors, as well as when using conditions according to Vigneron et al.[9] (dry benzene, presence of silver nitrate).
Failures of cyclization of C(5)-alkyl 2,3-dihydro-6*H*-1,4-oxazin-2-ones presumably reflect lower reactivity of the carbonyl group and higher vulnerability of the resulting ring system. This system seems to be stabilized enough in the derivatives **17–24** by the conjugative interaction of the endocyclic azomethine double bond, so that these derivatives could be isolated.
(13) This implies an *S* absolute configuration of the new chiral center C(5), if the inducing center C(3) possesses an *S* configuration. Detailed analysis of the CD spectra of these compounds will be published separately.
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Photolyses of 2-Azido-4-methoxy-6-(1-naphthyl)-1,3,5-triazines: Reactions of Singlet and Triplet 1,3,5-Triazinylnitrenes with Solvents

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Photochemical reactions of the title compounds with Me_2SO, acetone, and acetonitrile have been carried out. Photolyses of the triazinyl azides in acetone or acetonitrile gave the 1:1 cycloaddition products of the triazinylnitrene and the corresponding solvent molecule, aminotriazines, and unidentified polymeric products. In the case of Me_2SO, ylide, aminotriazine, and polymeric products were obtained. An electron-withdrawing substituent in the triazine nucleus accelerated the formation of addition product (or ylide) via the singlet nitrene. The chemical yields of the addition products varied depending upon solvents in the order of Me_2SO > acetone > acetonitrile. Aminotriazine is produced via the triplet nitrene.

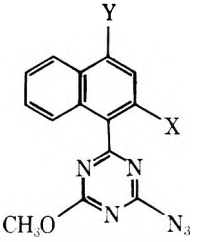
Recently, nitrene chemistry has been extensively studied and well established.[1] However, little is known about the triazinylnitrenes. Only the photocycloadditions of singlet triazinylnitrene with nitriles[2] and acetone[3] have been reported.

Triazine photochemistry involves interesting reactions: the photo-Smiles rearrangement,[4] the photo-Fries rearrangement,[5] the phototriazinilation,[6] and the intramolecular proton transfer in the excited state.[7] The 1,3,5-triazinyl group has an electron-withdrawing power, and formal charges at the nitrogen atoms of the triazine nucleus are very negative (ca. $-0.35 \sim -0.41$),[7] especially in the excited state. In addition, lone-pair electrons exist in the nitrogen atoms of the triazine nucleus. These electronic features may contribute to the photochemical reactions of triazines.

During the course of our studies on the triazine photochemistry, we have carried out the photolyses of 2-azido-4-methoxy-6-(1-naphthyl)-1,3,5-triazines in solution. This paper reports the reactions of singlet and triplet triazinylnitrenes with solvents (Me_2SO, acetone, and acetonitrile).

Results and Discussion

Preparation of 1,3,5-Triazine Derivatives. Azido-(1-naphthyl)-1,3,5-triazines employed are shown in Table I. Compounds **1, 2, 4,** and **5** were prepared by condensation of



1-Naphthylazido-1,3,5-triazines

the corresponding naphthalene derivatives with 2,4-dichloro-6-methoxy-1,3,5-triazine in the presence of $AlCl_3$ followed by treatment with sodium azide.[8] Compounds **3, 6, 7,** and **8** were synthesized by reactions of the corresponding 2- or 4-substituted 1-naphthylmagnesium bromide with cyanuric chloride followed by treatments with sodium methoxide and sodium azide.

Decomposition Quantum Yields of Azidotriazines. When the azidotriazines were irradiated with a high-pressure mercury lamp, a spectral change was observed with a lapse of time, suggesting that a clean photochemical reaction took place. The decomposition quantum yields of the azidotriazines were measured in cyclohexane at 254 nm using a low-pressure mercury lamp (Table II). Dissolved oxygen did not affect the quantum yields.

Photochemical Reactions of Azido-1,3,5-triazines. Reactions with Acetone. Photolyses of azidotriazines in acetone gave the 1:1 cycloaddition product of triazinylnitrene and acetone, the corresponding aminotriazine, and unidentified polymeric products depending upon the substituent Y in the naphthalene nucleus. These results are listed in Table III. The substituent in the naphthalene nucleus, especially the hydroxy group capable of forming an intramolecular hydrogen bond, was found to affect the photochemical reaction of azide. In the cases of compounds **1** and **2,** aminonaphthyltriazines which would result from the hydrogen-abstraction reaction by triplet nitrene were the major products, while in the cases of other azidotriazines cycloaddition products, which are considered to be produced via the electrophilic attack of singlet nitrene upon the carbonyl oxygen of acetone,[3] were the major product. It seems that the yield of the cycloaddition product increases with increasing the electron-withdrawing power of Y. That is, the electron-withdrawing substituent increases the electrophilic reactivity of singlet nitrene.

In the case of compound **1,** the reaction took place very selectively and the only product obtained was the corresponding amine resulting from the triplet nitrene. It is well known that an intramolecular hydrogen bond is formed in o-hydroxyaryltriazines. Therefore, in compound **1** a good coplanarity between two nuclei (naphthalene and triazine) would be expected due to the formation of the intramolecular hydrogen bond. This structure is responsible for an electron migration from the naphthalene ring to the triazine nucleus, and consequently the electrophilic reactivity of the singlet nitrene may decrease. As a result, the intersystem crossing $^1N \rightarrow {}^3N$ is dominant compared with the reaction of singlet nitrene with solvents.[9] Thus, instead of the photoproduct yielded from singlet nitrene, the product from triplet nitrene (aminotriazine) was obtained as the major product. In this case, however, an opposite effect which may decrease electron density at the proper nitrogen atom in the triazine nucleus through the intramolecular hydrogen bonding is also considered. However, the experimental results show that the former effect is predominant; the result described above may be one of a few examples of the remarkable effect of an intramolecular hydrogen bond upon photoreactivity.

The assumptions described above may be supported by the following facts that in the photolyses of azidotriazines in acetonitrile: (1) a cycloaddition product of triazinylnitrene and acetonitrile in a molar ratio of 1:1 is obtained when two substituents in the triazine nucleus are methoxyl groups;[2] (2) however, in the presence of benzophenone, which acts as a triplet sensitizer, only aminotriazine is obtained.[10] Similarly, only aminotriazine is obtained in the direct photolysis of 2-azido-4,6-bis(dimethylamino)triazine in acetonitrile,[10] indicating that the presence of two strong electron-donating

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Table I. Derivatives of Azido-1-naphthyl-1,3,5-triazine

Registry no.	Compd	X	Y	Mp, °C	Anal., % Found	Anal., % Calcd	UV[e] λ_{max}, nm	UV[e] $\epsilon \times 10^{-4}$	NMR,[f] δ_{ppm}
59336-44-6	1	OH	H[a]	163–164[b]	C, 57.25 H, 3.44 N, 28.45	57.14 3.43 28.56	375	1.2	4.18 (s, 3 H), 7.60 (m, 5 H), 9.57 (d, 1 H), 13.9 (br)
59336-45-7	2	H	OH[a]	198–199[b]	C, 57.24 H, 3.44 N, 28.62	57.14 3.43 28.56	346	1.7	4.07 (s, 3 H), 7.07 (d, 2 H), 7.60 (m, 2 H), 8.40 (m, 2 H), 9.30 (m, 1 H), 11.15 (br, 1 H)
59336-46-8	3	H	H[a]	98–99[c]	C, 60.75 H, 3.64 N, 30.87	60.42 3.62 30.20	324	1.3	4.10 (s, 3 H), 7.57 (m, 3 H), 8.27 (m, 2 H), 8.40 (d, 1 H), 9.07 (m, 1 H)
65103-10-8	4	OCH_3	H	136–137[c]	C, 58.26 H, 3.92 N, 27.41	58.44 3.62 27.26	337	0.55	3.92 (s, 3 H), 4.13 (s, 3 H), 7.42 (m, 4 H), 7.88 (m, 2 H)
65103-11-9	5	H	OCH_3	109–110[d]	C, 58.04 H, 3.91 N, 27.48	58.44 3.92 27.26	346	2.0	3.95 (s, 3 H), 4.07 (s, 3 H), 6.73 (d, 1 H), 7.50 (m, 2 H), 8.38 (m, 2 H), 9.29 (m, 1 H)
65103-12-0	6	CH_3	H	88–89[c]	C, 61.33 H, 4.13 N, 28.51	61.63 4.14 28.76	308	0.39	2.40 (s, 3 H), 4.10 (s, 3 H), 7.47 (m, 4 H), 7.87 (m, 2 H)
65103-13-1	7	H	CH_3	131–132[d]	C, 61.40 H, 4.12 N, 28.46	61.63 4.14 28.76	332	1.4	2.73 (s, 3 H), 4.12 (s, 3 H), 7.50 (m, 3 H), 8.03 (m, 1 H), 8.30 (d, 1 H), 9.12 (m, 1 H)
65103-14-2	8	H	Cl	113–114[d]	C, 53.60 H, 2.89 N, 26.51	53.77 2.90 26.87	327	1.4	4.17 (s, 3 H), 7.62 (m, 3 H), 8.33 (m, 2 H), 9.10 (m, 1 H)

[a] Reference 8. [b] Solvent for recrystallization benzene. [c] Solvent for recrystallization ligroin. [d] Solvent for recrystallization benzene–ligroin. [e] Measured in cyclohexane. [f] Measured in $CDCl_3$.

Table II. Decomposition Quantum Yields Φ_{decomp} of Azido-(1-naphthyl)-1,3,5-triazines in Cyclohexane at 254 nm and 25 °C[a]

Compd	Substituent X	Substituent Y	Φ_{decomp}
1	OH	H	0.2 ± 0.1
2	H	OH	0.3 ± 0.1
3	H	H	0.2 ± 0.1
4	OCH_3	H	0.1 ± 0.1
5	H	OCH_3	0.4 ± 0.1
6	CH_3	H	0.7 ± 0.1
7	H	CH_3	0.4 ± 0.1
8	H	Cl	0.4 ± 0.1

[a] The quantum yields were measured in the initial stages of the photolyses (about 10% decomposition). The initial concentration of azidotriazines was 1×10^{-2} M in cyclohexane.

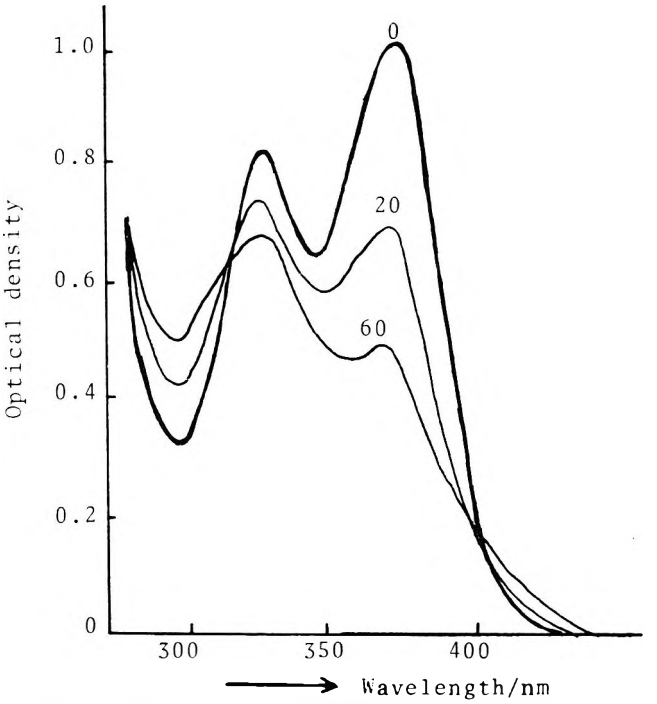


Figure 1. Spectral change of an acetonitrile solution of 2-azido-4-methoxy-6-(2-hydroxy-1-naphthyl)-1,3,5-triazine (1) by irradiation with a high-pressure mercury lamp. Numbers refer to time at a measurement in seconds.

groups in the triazine nucleus lowers the electrophilic reactivity of singlet nitrene very much. The cycloaddition product is known to result from the electrophilic attack of singlet triazinylnitrene upon the nitrogen atom of acetonitrile.[2]

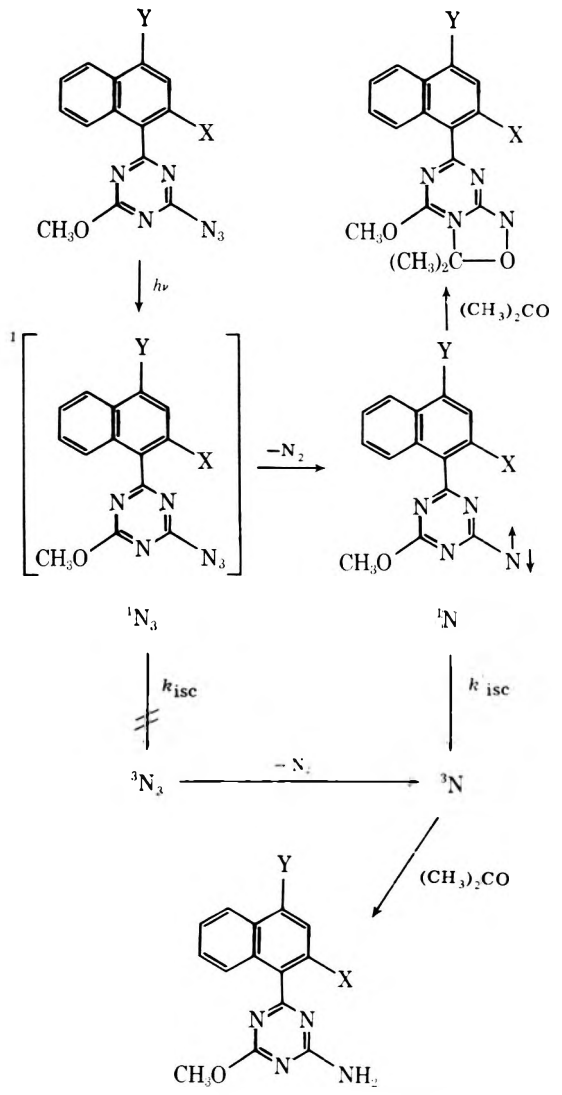
From quenching experiments, phenyl azide in the excited singlet state decomposes to the singlet nitrene and nitrogen ($^1\Sigma_g^+$).[11] By means of laser spectroscopy, it has been shown that the direct photodecomposition of 1-azidopyrene occurs through $^1N_3 \rightarrow {}^1N \rightarrow {}^3N$.[12] In the photolysis of 2-azido-4,6-dimethoxy-1,3,5-triazine in nitriles, the singlet mechanism occuring through $^1N_3 \rightarrow {}^1N \rightarrow$ adduct is also shown.[2]

Thus, the reaction pathway in the azidotriazine–acetone system is similarly accounted for by Scheme I, where ^1N and ^3N denote the singlet and triplet nitrenes, respectively. As for compound 1, the intersystem crossing k'_{isc} is faster than the reaction of ^1N with acetone.

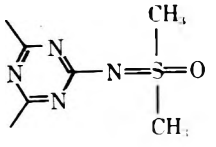
Photolyses of Azidotriazines in Me_2SO. In the photolyses of azido(1-naphthyl)triazines in Me_2SO, the corresponding ylide, aminotriazine, and unidentified polymeric products were obtained (Table IV).

In the cases of compounds 1 and 2, both ylide and aminotriazine were obtained; however, in other cases no aminotriazine was detected. The photoproducts of ylide and aminotriazine seem to be yielded by the reactions of singlet and

Scheme I

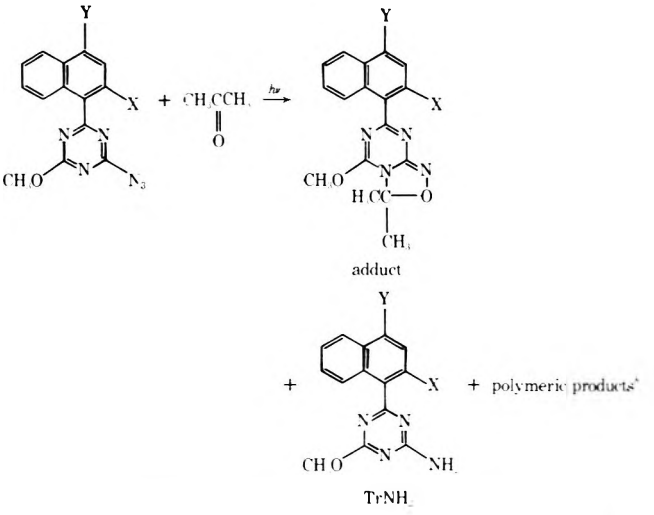


triplet nitrenes with Me_2SO, respectively. On the whole, the results in Table IV show that the photolysis in Me_2SO occurs in a pattern similar to that in acetone. However, the reaction of singlet nitrene with Me_2SO may proceed more readily than that in acetone. In Me_2SO, the reaction stopped at the stage of ylide instead of the cycloaddition product.[13] The combination between the ring nitrogen and oxygen atoms to give the cycloaddition product would be difficult because the ylides from Me_2SO are considered to exist as sulfoximine derivatives.[14]



Photolyses of Azidotriazines in Acetonitrile. The photolyses of azidotriazines in acetonitrile also gave the 1:1 cycloaddition product of triazinylnitrene and acetonitrile, aminotriazine, and unidentified polymeric products; however, the cycloaddition product was obtained only in the case of compound 4 as shown in Table V. In this case, two aromatic nuclei would be twisted toward each other very much by the steric hindrance due to the o-methoxyl group, resulting in a decrease in the electron migration from the naphthalene ring to the triazine nucleus; in addition this $-I$ effect of the naphthyl group would decrease the electron density of the triazine nucleus. Therefore, the main reaction product results from the singlet nitrene.

Table III. Photochemical Reactions of Azidotriazines in Acetone[a]



Compd	X	Y	% adduct	% $TrNH_2$
1	OH	H	*c*	43
2	H	OH	18	30
3	H	H	50	5
4	OCH_3	H	63	*c*
5	H	OCH_3	50	*c*
6	CH_3	H	31	8
7	H	CH_3	32	5
8	H	Cl	68	*c*

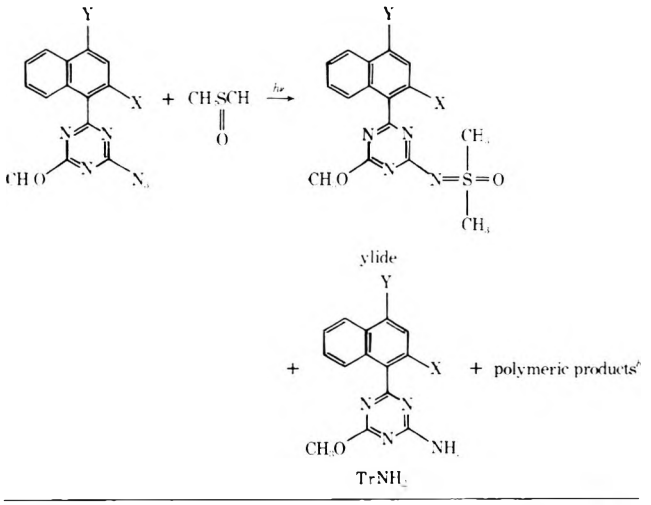
[a] Solutions of azidotriazines in acetone (0.1 g in 20 mL of acetone) were irradiated. Irradiation with a high-pressure mercury lamp was continued until the starting materials (azidotriazines) disappeared completely. It took about 2 days. [b] Unidentified dark brown polymeric products were produced in large amounts. [c] Undetected.

Although in the photolyses of azido(1-naphthyl)triazines in acetone, Me_2SO, and acetonitrile the addition product and/or aminotriazine was obtained as the major product in every case, the yield of the major product varied depending upon the solvent employed. Overall, the highest yields of addition products were obtained with Me_2SO, while acetonitrile gave the highest yields of amines. This difference in reactivity among the solvents employed may be attributed to a difference in the electron-donating power of solvents; for example, the sulfur atom in Me_2SO would be more electron donating than the oxygen atom in acetone (the 3p lone pair electrons of the sulfur atom should be much more electron donating than the 2p lone pair electrons of the oxygen atom). Thus, the electrophilic attack by singlet triazinylnitrene upon the sulfur atom of Me_2SO would take place more readily than that upon the carbonyl oxygen atom of acetone. As for acetone and acetonitrile, the former would be more electron donating in accord with their ionization potentials; the ionization potential of acetonitrile is known to be 1.23 eV[15] and that of acetone is 9.69 eV.[16] Thus, when compound 4 was irradiated in a mixture of Me_2SO, acetone, and acetonitrile, although all products obtained were resulted from the singlet triazinylnitrene, the yields of the addition products varied in the following order with respect to the solvents, supporting the assumption described above:

$$Me_2SO > \text{acetone} > \text{acetonitrile}$$

In conclusion, the reactions of singlet and triplet triazinylnitrenes produced by the photolyses of azido(1-naphthyl)triazines can be explained reasonably by Scheme II, where T-N_3 is the starting material, ^3D the triplet sensitizer

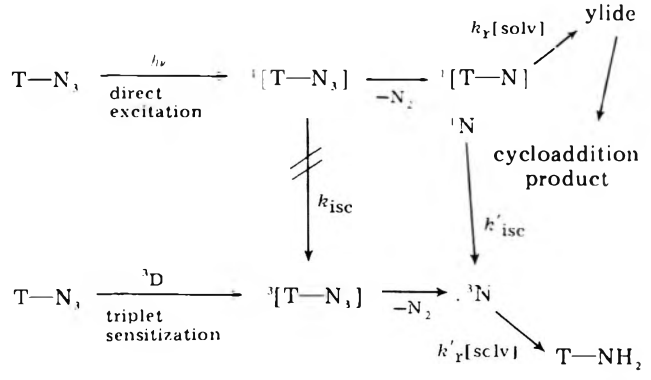
Table IV. Photochemical Reactions of Azidotriazines in Me_2SO[a]



Compd	X	Y	% ylide	% $TrNH_2$
1	OH	H	30	25
2	H	OH	25	27
3	H	H	55	c
4	OCH_3	H	43	c
5	H	OCH_3	54	c
6	CH_3	H	50	c
7	H	CH_3	54	c
8	H	Cl	63	c

[a] Solutions of azidotriazines in Me_2SO (2.0 g in 20 mL of Me_2SO) were irradiated with a high-pressure mercury lamp for 2 days; however 25–30% of the starting materials (azidotriazines) were recovered. [b] Unidentified polymeric products were produced in small amounts. [c] Undetected.

Scheme II



(e.g., benzophenone), and ^1N and ^3N the singlet and triplet triazinylnitrenes, respectively.

The overall reaction is governed by the relative rate of the electrophilic attack (k_r[solv]) to that of intersystem crossing k'_{isc},[9] which depends upon the electronic property of the substituent in the naphthalene nucleus on one hand and the electron-donating power of the solvent on the other hand.

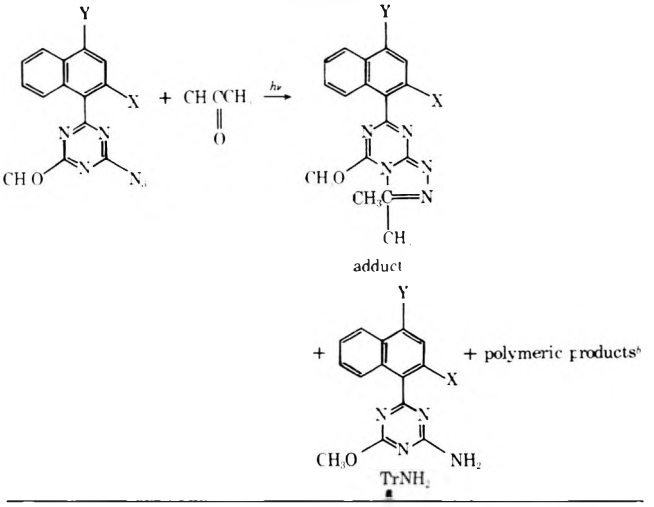
Thus, when k_r[solv] > k'_{isc}, the cycloaddition product or ylide is the major product, while aminotriazine becomes the main product when k_r[solv] < k'_{isc}.

Experimental Section

All the melting points are uncorrected. The identification of the reaction products was performed by means of NMR, IR, UV, and MS spectra, by elemental analyses, and by a mixed melting point test with an authentic sample.

Materials. A typical preparation by the Friedel–Crafts reaction of chlorotriazines with naphthalene derivatives is shown in the case of compound **4**. Compounds **1**, **2**, and **5** were prepared by treating the corresponding chlorotriazine derivatives with sodium azide.[8]

Table V. Photochemical Reactions of Azidotriazines in Acetonitrile[a]



Compd	X	Y	% adduct	% $TrNH_2$
1	OH	H	c	30
2	H	OH	c	21
3	H	H	c	25
4	OCH_3	H	23	6

[a] Solutions of azidotriazines in acetonitrile (2.0 g in 20 mL of acetonitrile) were irradiated with a high-pressure mercury lamp for 1 week; however 45–50% of the starting materials (azidotriazines) were recovered. [b] Unidentified dark brown polymeric products were produced in large amounts. [c] Undetected.

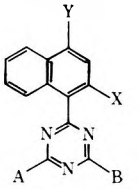
2-Azido-4-methoxy-6-(2-methoxy-1-naphthyl)-1,3,5-triazine (4). A solution of 45.0 g (0.29 mol) of β-methoxynaphthalene in 300 mL of chloroform was added drop by drop into a mixture of 52.0 g (0.29 mol) of 2,4-dichloro-6-methoxy-1,3,5-triazine, 38.8 g (0.29 mol) of powdered aluminium chloride, and 800 mL of chloroform at room temperature. The mixture was stirred at 40 °C for 24 h; then the reaction mixture was poured into 1 L of ice water containing 250 mL of a concentrated hydrochloric acid solution. After the chloroform layer was washed with water, chloroform was distilled off, and the residue was purified by column chromatography on silica gel using a mixture of benzene and ligroin (10:1 by volume) to give an analytical sample of 2-chloro-4-methoxy-6-(2-methoxy-1-naphthyl)-1,3,5-triazine in a yield of 24%: mp 142–143 °C.

A solution of 7.8 g (0.116 mol) of sodium azide in 60 mL of water was added drop by drop into a solution of 10 g (0.033 mol) of 2-chloro-4-methoxy-6-(2-methoxy-1-naphthyl)-1,3,5-triazine in 300 mL of dioxane at room temperature. After stirring at 45 °C for 7 h, the reaction mixture was poured into 1 L of water. The precipitate thus obtained was filtered, dried, and purified by recrystallization from lingoin to give an analytical sample of compound **4** in a yield of 98%: mp 136–137 °C.

A typical preparation by the Grignard reaction of 1-naphthylmagnesium halides with chlorotriazines is shown in the case of compound **6**. A solution obtained by the reaction of 30.0 g (0.136 mol) of 2-methyl-1-bromonaphthalene with 3.30 g (0.136 mol) of magnesium in a mixture of 250 mL of diethyl ether and 150 mL of tetrahydrofuran was added drop by drop into a solution of 25.0 g (0.136 mol) of cyanuric chloride in 350 mL of diethyl ether at room temperature. After stirring for 5 h at room temperature, the mixture was poured into 1 L of ice water containing 200 mL of concentrated hydrochloric acid. The ether layer was washed with water, then the solvent was removed by distillation and the residue was purified by column chromatography on silica gel using a mixture of benzene and ligroin (2:1 by volume) to give 2,4-dichloro-6-(2-methyl-1-naphthyl)-1,3,5-triazine in a yield of 23%: mp 141–142 °C.

A solution obtained by dissolving 0.4 g (0.0174 mol) of sodium in 50 mL of methanol was added drop by drop into a solution of 5.0 g (0.0174 mol) of 2,4-dichloro-6-(2-methyl-1-naphthyl)-1,3,5-triazine in a mixture of methanol (50 mL) and dioxane (100 mL). The reaction mixture was stirred for 2 h at room temperature, then was poured into 500 mL of ice water and extracted with chloroform. After the solvent was removed by distillation, the reaction product was purified by

Table VI. Derivatives of Chloro(1-naphthyl)-1,3,5-triazine



Registry no.	A	B	X	Y	Mp, °C	Solvent for recrystallization	Anal., % Found C	Found H	Found N	Calcd C	Calcd H	Calcd N
65103-15-3	OCH_3	Cl	OCH_3	H	142–143	Ligroin	59.95	4.03	13.75	59.70	3.98	13.93
65103-16-4	OCH_3	Cl	H	OCH_3	135–136	Benzene–ligroin	59.57	4.15	14.11	59.70	3.98	13.93
65103-17-5	Cl	Cl	CH_3	H	141–142	Ligroin	58.10	3.22	14.28	57.93	3.10	14.48
4446-43-9	Cl	Cl	H	CH_3	173–174	Benzene–ligroin	57.78	3.33	14.56	57.93	3.10	14.43
65103-18-6	OCH_3	Cl	CH_3	H	90–91	Ligroin	63.24	4.43	14.63	63.05	4.20	14.71
65103-19-7	OCH_3	Cl	H	CH_3	132–133	Benzene–ligroin	63.03	4.35	14.57	63.05	4.20	14.71
65103-20-0	Cl	Cl	H	Cl	135–136	Benzene–ligroin	50.43	2.05	13.66	50.24	1.93	13.53
65102-89-8	OCH_3	Cl	H	Cl	120–121	Benzene–ligroin	54.83	3.12	13.84	54.90	2.94	13.73

Table VII. 2-Amino-4-methoxy-6-(2- or 4-substituted-1-naphthyl)-1,3,5-triazines

Registry no.	X	Y	Mp, °C	Solvent for recrystallization	Anal., % Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N	MS, m/e
65102-90-1	OH	H	225–226	Benzene	62.80	4.67	20.78	62.68	4.51	20.89	268
65121-39-3	H	OH	215–216	Benzene	62.97	4.60	20.71	62.68	4.51	20.89	268
65102-91-2	H	H	220–221	Benzene	66.35	4.71	22.01	66.65	4.79	22.21	252
65102-92-3	OCH_3	H	221–222	Benzene	63.98	4.87	19.51	63.82	5.00	19.85	282
65102-93-4	CH_3	H	218–219	Benzene	67.98	5.31	20.96	67.65	5.30	21.04	266
65102-94-5	H	CH_3	220–221	Benzene	67.92	5.28	20.78	67.65	5.30	21.04	266

Table VIII. 1:1 Adducts of 4-Methoxy-6-(2- or 4-substituted-1-naphthyl)-1,3,5-triazin-2-ylnitrene and Acetone or Acetonitrile

Registry no.	Substituent X	Substituent Y	Mp, °C	Solvent for recrystallization	Anal., % Found	Anal., % Calcd	MS, m/e	NMR, δ_{ppm}
					Acetone			
65102-95-6	H	OH	221–222	Benzene	C, 62.96 H, 5.16 N, 17.59	62.95 4.97 17.28	324	[a] 1.73 (s, 6 H), 4.15 (s, 3 H), 6.98 (d, 1 H), 7.57 (m, 2 H), 8.33 (m, 3 H), 9.22 (m, 1 H)
65102-96-7	H	H	177–178	Benzene	C, 66.70 H, 5.24 N, 18.42	66.22 5.23 18.17	308	[a] 1.75 (s, 6 H), 4.12 (s, 3 H), 7.58 (m, 3 H), 8.07 (m, 3 H), 8.93 (m, 1 H)
65102-97-8	OCH_3	H	196–197	Benzene	C, 64.02 H, 5.32 N, 16.62	63.89 5.36 16.58	338	[a] 1.77 (s, 6 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 7.95 (m, 6 H)
65102-98-9	H	OCH_3	173–174	Benzene	C, 63.40 H, 5.41 N, 16.57	63.89 5.36 16.58	338	[b] 1.78 (s, 6 H), 4.03 (s, 3 H), 4.13 (s, 3 H), 6.83 (d, 1 H), 7.52 (m, 2 H), 8.38 (m, 2 H), 9.33 (m, 1 H)
65102-99-0	CH_3	H	147–148	Benzene	C, 67.09 H, 5.72 N, 17.81	67.06 5.63 17.38	322	[b] 1.83 (s, 6 H), 2.52 (s, 3 H), 4.00 (s, 3 H), 7.42 (m, 3 H), 7.80 (m, 3 H)
65103-00-6	H	CH_3	167–168	Benzene	C, 67.15 H, 5.61 N, 17.42	67.06 5.63 17.38	322	[b] 1.80 (s, 6 H), 2.72 (s, 3 H), 4.13 (s, 3 H), 7.42 (m, 3 H, 8.08 (m, 2 H), 9.17 (m, 1 H)
65103-01-7	H	Cl	145–146	Benzene	C, 59.83 H, 4.45 N, 16.55	59.57 4.41 16.34	342	[b] 1.83 (s, 6 H), 4.18 (s, 3 H), 7.66 (m, 3 H), 8.33 (m, 2 H), 9.20 (m, 1 H)
					Acetonitrile			
65103-02-8	OCH_3	H	135–136	Benzene	C, 63.24 H, 4.73 N, 21.61	63.54 4.70 21.80	321	[a] 3.22 (s, 3 H), 3.87 (s, 3 H), 3.95 (s, 3 H), 7.50 (m, 5 H), 8.05 (m, 1 H)

recrystallization from ligroin to give an analytical sample of 2-chloro-4-methoxy-6-(2-methyl-1-naphthyl)-1,3,5-triazine (mp 90–91 °C) in a yield of 84%.

2-Chloro-4-methoxy-6-(2-methyl-1-naphthyl)-1,3,5-triazine was treated with sodium azide in a manner similar to that of described above to give the corresponding azido-1,3,5-triazine in a yield of 92% (mp 88–89 °C).

Analytical data of new compounds of chlorotriazine type were listed in Table VI.

Acetone and Me_2SO (G.R. grade) were used without further puri-

Table IX. Photochemical Reaction Products (Ylides) of 2-Azido-4-methoxy-6-(2- or 4-substituted-1-naphthyl)-1,3,5-triazines with Me_2SO

Registry no.	X	Y	Mp, °C	Solvent for recrystallization	Anal., % Found	Anal., % Calcd	MS, *m/e*	NMR (Me_2SO-d_6), δ_{ppm}
65103-03-9	OH	H	214–215	Acetone	C, 55.69 H, 4.67 N, 16.25	55.80 4.68 16.27	344	3.50 (s, 6 H), 4.06 (s, 3 H), 7.75 (m, 6 H), 9.27 (m, 1 H)
65103-04-0	H	OH	152–153	Benzene	C, 55.71 H, 4.42 N, 16.36	55.80 4.68 16.27	344	3.55 (s, 6 H), 4.02 (s, 3 H), 7.03 (m, 1 H), 7.58 (m, 2 H), 8.27 (m, 2 H), 9.25 (m, 1 H), 10.83 (m, 1 H)
65121-40-6	H	H	164–165	Benzene–ligroin	C, 58.89 H, 5.21 N, 17.63	58.52 4.91 17.06	328	3.58 (s, 6 H), 4.03 (s, 3 H), 7.63 (m, 3 H), 8.08 (m, 3 H), 9.13 (m, 1 H)
65103-05-1	OCH_3	H	193–194	Benzene	C, 57.15 H, 5.05 N, 15.54	56.97 5.06 15.63	358	3.53 (s, 6 H), 3.90 (s, 3 H), 3.98 (s, 3 H), 7.50 (m, 4 H), 8.10 (m, 1 H), 9.15 (m, 1 H)
65103-06-2	H	OCH_3	194–195	Benzene	C, 57.43 H, 5.10 N, 15.65	56.97 5.06 15.63	358	3.55 (s, 6 H), 4.00 (s, 3 H), 4.05 (s, 3 H), 7.12 (d, 2 H), 7.58 (m, 2 H), 8.30 (m, 2 H), 9.17 (m, 1 H)
65103-07-3	CH_3	H	218–219	Benzene	C, 59.43 H, 5.47 N, 16.45	59.63 5.30 16.36	342	2.33 (s, 3 H), 3.52 (s, 6 H), 3.98 (s, 3 H), 7.50 (m, 4 H), 7.97 (m, 2 H)
65103-08-4	H	CH_3	219–220	Benzene	C, 59.56 H, 5.30 N, 16.42	59.63 5.30 16.36	342	2.76 (s, 3 H), 3.58 (s, 6 H), 4.03 (s, 3 H), 7.60 (m, 3 H), 8.13 (d, 2 H), 9.00 (m, 1 H)
65103-09-5	H	Cl	140–141	Benzene	C, 53.10 H, 4.33 N, 15.40	52.96 4.17 15.44	362	3.58 (s, 6 H), 4.05 (s, 3 H), 7.80 (m, 3 H), 8.20 (m, 2 H), 9.05 (m, 1 H)

fication. Acetonitrile (reagent grade) was purified by the usual method.[17] Cyclohexane (G.R. grade) was further purified by passing it through a silica gel column and by distillation.

Light Source and Actinometry. A high-pressure mercury lamp (a Richosa 100-W UVL-100HA) was used for photolyses. Nitrogen gas was bubbled through the solutions during the photolyses. A low-pressure mercury lamp (30 W) with a Vycor glass filter was used as the 254-nm radiation source. The decomposition quantum yields for the starting materials were measured in cyclohexane at 254 nm and 25 °C. Actinometry was carried out using a ferric oxalate solution (0.006 M).[18]

Reaction Products. After a long irradiation of solutions of azidotriazines in acetone, acetonitrile, and Me_2SO with a high-pressure mercury lamp (see the Tables III–V), the reaction mixtures were evaporated. Then the photoproducts were separated and purified by column chromatography on silica gel using a mixture of benzene and acetone as the developing solvent (the ratio of the two solvents was changed depending upon the photoproducts obtained).

2-Amino-4-methoxy-6-(2- or 4-substituted-1-naphthyl)-1,3,5-triazines. Analytical data of aminotriazines were listed in Table VII. These compounds were also confirmed by a mixed melting point test with authentic samples prepared by condensation of the corresponding chlorotriazines with ammonia under pressure.

Adducts of Triazinylnitrene and Acetone, Acetonitrile, or Me_2SO. Analytical data of the adducts were listed in Tables VIII and IX.

Adducts of Triazinylnitrene and Acetone. A typical example is noted below in the case of the adduct of acetone and methoxy(1-naphthyl)triazinylnitrene (X = Y = H); *m/e* of 308 agrees with the predicted value. NMR spectra support the constitution proposed: δ 1.75 (2-CH_3), 4.12 (-OCH_3), 7.58 and 8.07 (aromatic protons, 6 H), 8.93 (H of 8-position of the naphthalene nucleus, 1 H). IR spectrum of this compound (measured in potassium disk) lacks a peak of carbonyl group.

Adducts of Triazinylnitrene and Acetonitrile. MS and NMR spectra support the proposed structure: *m/e* 321; NMR δ 3.22 (-CH_3), 3.87 (-OCH_3), 3.95 (-OCH_3), 7.50 (aromatic protons, 5 H), 8.05 (H of 8-position of the naphthalene nucleus, 1 H). IR spectrum of this adduct lacks a peak of -C≡N group.

Adducts of Triazinylnitrene and Me_2SO. A typical example is noted below in the case of the adduct of (4-methyl-1-naphthyl)triazinylnitrene and Me_2SO (X = H, Y = -CH_3): *m/e* of 342 agrees with the predicted value. NMR spectra [δ 2.76 (-CH_3), 3.58 (2-CH_3), 4.03 (-OCH_3), 7.60 and 8.13 (aromatic protons), 9.00 (H of 8-position of the naphthalene nucleus)] agree with the constitution proposed. IR spectrum of this compound involves peaks assignable to SO group (1015 cm^{-1}) and triazine nucleus (820 cm^{-1}).

Registry No.—Acetone, 67-64-1; acetonitrile, 75-05-8; Me_2SO, 67-68-5; β-methoxynaphthalene, 93-04-9; 2,4-dichloro-6-methoxy-1,3,5-triazene, 3638-04-8; sodium azide, 26628-22-8; 2-methyl-1-bromonaphthalene, 2586-62-1; cyanuric chloride, 108-77-0; 1-bromonaphthalene, 90-11-9; 1-bromo-4-methylnaphthalene, 6627-78-7; 1-bromo-4-chloronaphthalene, 53220-82-9.

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Methylation of Protomeric Ambident Nucleophiles with Methyl Fluorosulfonate: A Regiospecific Reaction

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Methylation of 15 protomeric ambident nucleophiles with methyl fluorosulfonate has been found to occur regiospecifically at the heteroatom remote from the mobile proton. In most cases the fluorosulfonate salts thus obtained can be isolated, identified by ^{1}H NMR spectroscopy, and converted to the neutral methylated derivatives by aqueous base. The compounds studied include five of the nine possible systems X=YZH ⇄ HXY=Z, in which Y is carbon and X and Z are oxygen, nitrogen, and/or sulfur. In 12 cases the reaction is synthetically useful, although it is sometimes necessary to remove the excess methyl fluorosulfonate prior to treatment with base. Three cases give mixtures of methylated products, a result established for the case of 2-pyridone to be due to proton transfer from the initial regiospecifically formed salt.

The alkylation of protomeric tautomers is of interest in a wide variety of chemical and biochemical studies.[1,2] More detailed understanding and better control of such reactions would be useful.

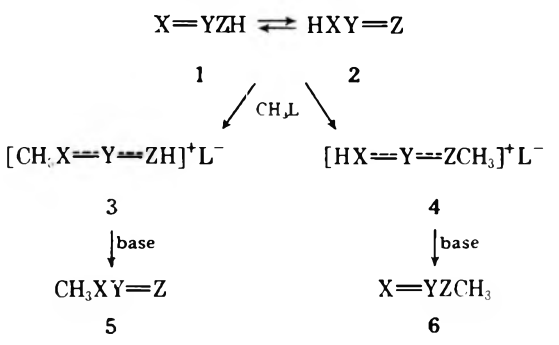
A generalized case is shown in Scheme I for methylation of the ambident protomeric nucleophiles **1** and **2** to give the salts **3** and **4**. Reaction of **3** and **4** with a base would provide the methylated isomers **5** and **6**. It is well-recognized that there is not necessarily any correspondence between the relative amounts of the protomeric reactants, **1** and **2**, and the isomeric products, **3** and **4** or **5** and **6**. Recent analyses of such reactions have been appropriately cautious.[1,3-6]

If X and Z are heteroatoms, proton transfer would be expected to be several orders of magnitude more rapid than methylation, and the relative rates of formation of **3** and **4** would then be determined solely by the relative transition-state energies leading to these cations.[7,8] If **3** and **4** are stable under the conditions of their formation, subsequent deprotonation would provide **5** and **6** in a ratio which has been determined by the relative transition-state energies leading to **3** and **4**. Reaction profiles showing product control under the Curtin–Hammett principle[7] in which the ratios of **3** and **4** could be greater or less than one are illustrated in Figure 1.

Nonetheless, the possibility does exist that there might be a circumstantial relationship between the ground-state energies of **1** and **2** and the transition states for their alkylation. For example, the bonding features which make **1** of lower energy than **2** could persist in the respective transition states (Figure 1a). In that case, cation **3** would be predominant and the subsequent isomer **5**, in which the alkyl group is attached to the heteroatom remote from the mobile proton in the major tautomer, would be produced after proton removal by a base. While this guide would be at best a *qualitative* indication of the position of alkylation, it is interesting that if the transition-state energy difference were >2 kcal/mol (at 25 °C) an effectively regiospecific alkylation of the tautomeric system would result. Formally the proton would appear to be a directing group if the profile of Figure 1a were followed. In fact, a number of cases exist which follow such a qualitative course.[1,3,5,9]

It should be emphasized that quantitative correlation of the

Scheme I



tautomeric ratio and the ratio of alkylated products is neither expected[6,7] nor observed, as careful studies of 5-nitroimidazole by Ridd[3] and of 3-hydroxyisothiazole by Crow[4] have shown. Moreover, our above suggestion of possible qualitative generality for the reaction path of Figure 1a might well be considered naive by the following argument. If isomers **1** and **2** undergo protonation to give a common product, the difference in the ground-state energies of **1** and **2** can be considered to reflect the difference in basicity of the atoms X and Z. If that basicity difference reflects a parallel difference in the nucleophilicity of these atoms in the respective transition states for alkylation, the suggested regiospecificity would not be observed.[3,10] On a practical level, the assumptions that the salts **3** and **4** will be stable and that the neutral tautomers will be reactive nucleophiles might not be valid.

In order to explore the possibility that the pathway of Figure 1a could be followed for more than a few cases, we have investigated the reactions of 15 protomeric ambident nucleophiles and methyl fluorosulfonate.[11] This highly reactive readily soluble methylating agent was chosen to maximize the possibilities that transition states would reflect the ground-state energies of the tautomers and that the reaction could be driven, and the initially formed salts stabilized, by precipitation from a nonpolar solution. In general, the regiospecific course suggested by Figure 1a is followed, although synthetic complications arise due to the instabilities of the initially formed salts to the reaction conditions for three cases.[12-14]

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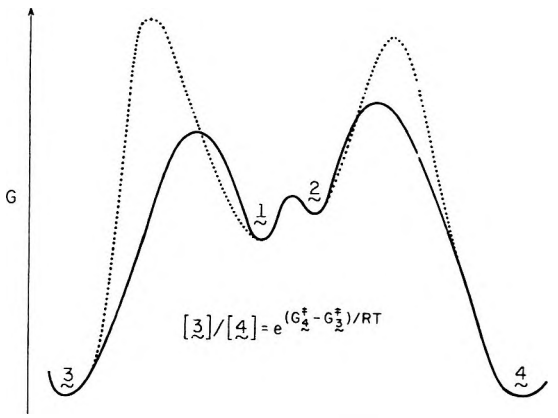


Figure 1. Illustrative reaction profiles for Scheme I. (a) Solid line: the transition-state energy difference is of the same sign as the ground-state energy difference; [3]/[4] > 1. (b) Dotted line: the transition-state energy difference is of opposite sign to the ground-state energy difference; [3]/[4] < 1.

Results and Discussion

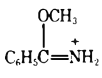
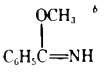
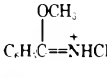
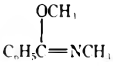
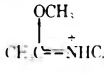
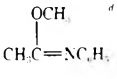
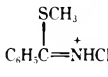
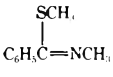
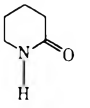
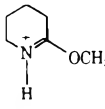
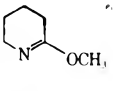
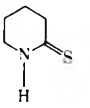
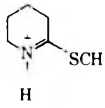
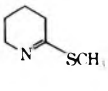
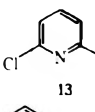
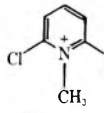
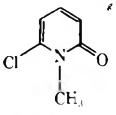
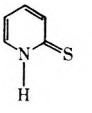
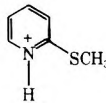
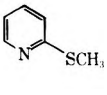
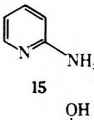
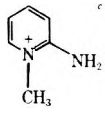
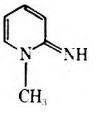
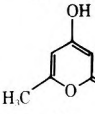
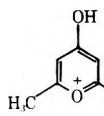
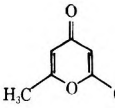
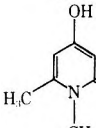
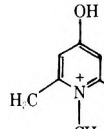
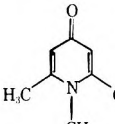
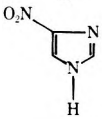
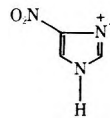
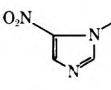
If the major product of reaction of a series of ambident protomeric tautomers with methyl fluorosulfonate is the isomer in which the methyl group is bonded to the heteroatom remote from the mobile proton in the major tautomer, then the process of Figure 1a is followed qualitatively. In effect, for the conversion shown in Scheme I, the more stable tautomer 1 would be converted to **5** via **3**; such a regiospecific conversion could be synthetically valuable. The nucleophiles **7–18** shown in Table I follow the prescribed course for reactions at ambient temperature in <2 h. These compounds cover five of the nine possible cases representable by **1** and **2** in which X and Z are oxygen, nitrogen, and/or sulfur and Y is carbon. A second-order rate constant for the disappearance of **8** and the appearance of the corresponding fluorosulfonate of 2.9 (±0.8) × 10^{-4} M^{-1} s^{-1} was measured by ^1H NMR. The intermediate salts can be isolated and were spectroscopically characterized (Table IV) for seven of the cases in Table I. None of the isomers which would result from methylation at the heteroatom which bears the proton in the major tautomer is detected in these cases. The yields of alkylated products (Table I) are usually high and generally superior to those of alternative procedures. The fact that the less stable, and therefore prospectively more reactive, isomer of **5** ⇆ **6** is produced readily and in high yield suggests that these reactions may be useful for sequences in which further conversions are important.

The conversions of the amides and thioamides **7–12** and **14** to the corresponding imidates by reactive alkylating agents are well precedented.[9] In fact Julia and Ryan have reported such conversions with methyl fluorosulfonate.[9i] The reactions of 2-aminopyridine (**15**) and 5-nitroimidazole (**18**) also follow previously known courses. Comparison of **13, 14,** and **15** suggests that the presence of a pyridine ring does not affect the outcome of the reaction.[15] Precipitation of the intermediate salt occurs in 6 of the 12 cases shown in Table I so that driving force does not appear to be required for successful reaction.

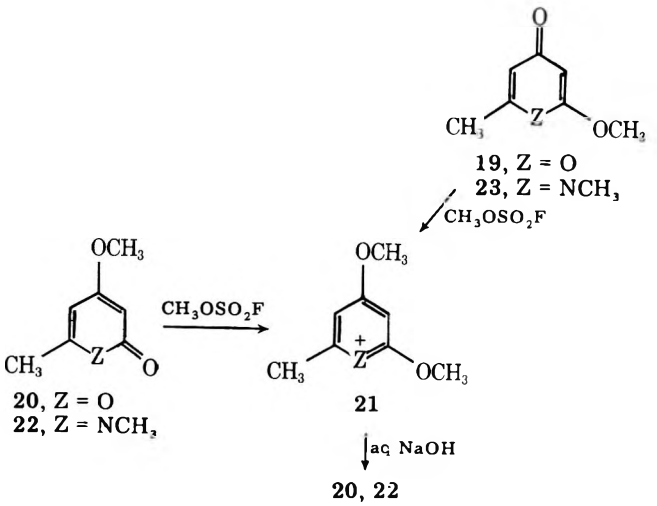
The conversion of 4-hydroxy-6-methyl-2-pyrone (**16**) to 2-methoxy-6-methyl-4-pyrone (**19**) in 98% yield provides our best example of the value of this procedure in convenience and yields. Alternative conversions, which involve reaction of **16** with diazomethane followed by separation of **19** from **20**[16] or blocking of the hydroxyl function of **16** with the trimethylsilyl group followed by methylation,[17] provide **19** in ~20% yield.

The possibility that the reactions of **16** and 4-hydroxy-1,6-dimethyl-2-pyridone (**17**) proceeded by formation of the polymethylated salts **21** was discounted in two ways. In the first place, the precipitated salts can be isolated and characterized by ^1H NMR as monomethylated species (Table IV). Secondly, formation of the dialkylated salts **21** from the respective isomeric pairs **19** ⇆ **20** and **22** ⇆ **23** followed by basic hydrolysis gives the products **20** and **22**, respectively.

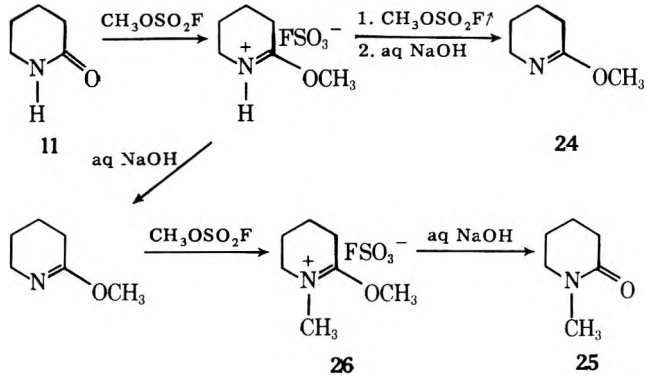
Table I. Reactions of Protomeric Tautomers with Methyl Fluorosulfonate Which Provide Products of Methylation at the Heteroatom Remote from the Mobile Proton

Reactant	Registry no.	Intermediate cation	Product[a]
 7	55-21-9		 [b]
 8	613-93-4	 [c]	
 9	103-84-4		 [d]
 10	5310-14-5		
 11	675-20-7		 [e,f]
 12	13070-01-4	 H	
 13	16879-02-0	 [c]	 [g]
 14	2637-34-5	 H	
 15	504-29-0	 [c]	
 16	675-10-5	 [c]	
 17	6052-75-1	 [c]	
 18	2075-46-9	 [c]	 [h]

[a] Yields are 98–100% unless otherwise indicated. [b] The yield estimated by NMR is 85% and the isolated yield is 41%. [c] The fluorosulfonate salt precipitates during reaction. [d] The yield estimated by NMR is 80% and the isolated yield is 37%. [e] The isolated yield is 78%. [f] The same product could be produced in 82% by reaction with 1 equiv of trimethyloxonium fluoroborate in methylene chloride followed by treatment of that solution with aqueous base. [g] The yield is 78%. [h] The isolated yield is 71%.

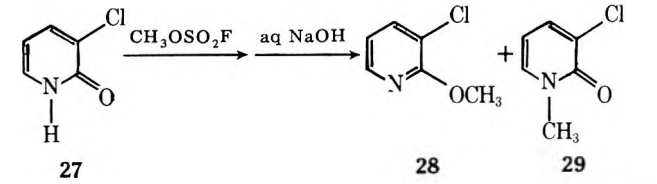


The manner in which the reaction is quenched can be critical. For example, although reaction of **11** with methyl fluorosulfonate followed by removal of the excess methylating agent and treatment with aqueous base provides **24** in 78%



yield, if the reaction is quenched with aqueous base without removal of the excess methylating agent only the amide **25** is observed (Table II). Since the expected oxygen-methylated fluorosulfonate salt is formed in the first step (Table IV), base and excess methylating agent must convert this salt to the dimethylated salt **26**, which undergoes hydrolysis to **25**. Such a sequence is precedented by similar observations of Lüssi[18] with dimethyl sulfate.

A similar, potentially misleading result was observed with 3-chloro-2-pyridone (**27**). In this case reaction was unusually



slow and a mixture of products **28** and **29** with **28** predominant was obtained in moderate yield (Table III).[19] However, if the reaction was quenched without removal of excess methylating agent, **28** and **29** were produced in high yields with **29** the predominant isomer (Table III). The apparent explanation of these results is that in the presence of excess base and methylating agent unreacted **27** is methylated through the corresponding anion. Hence, both the rate and product distribution are very different from the reactions of the neutral species. This possibility was confirmed by the finding that addition of **27** to a mixture of methylene chloride, aqueous base, and excess methyl fluorosulfonate gave **28** and **29** in 92% yield in a ratio of 5:95 (Table III).

If the regiospecificity of the alkylations of protomeric ambident nucleophiles by methyl fluorosulfonate could be controlled by removal of excess methylating agent, the process might be of broad synthetic value. However, additional complications were revealed in our investigations of 2-pyridone and 4-pyridone (Table II). Reaction of 2-pyridone (**30**) with methyl fluorosulfonate followed by removal of excess reagent in vacuo gives <50% total yield of 2-methoxypyridine (**31**) and 1-methyl-2-pyridone (**32**) in a ratio which varies in

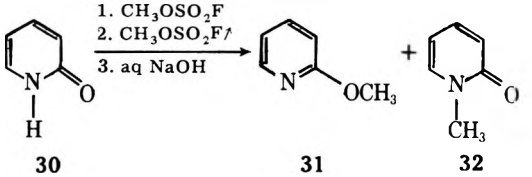
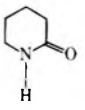
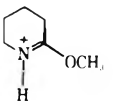
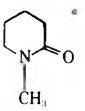
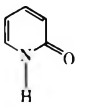
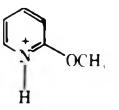
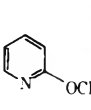
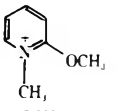
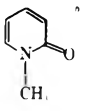
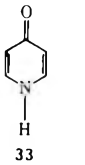
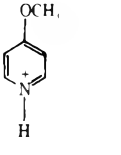
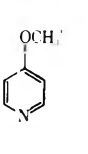
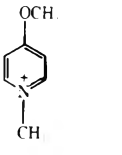
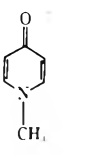


Table II. Methylations of Protomeric Tautomers with Methyl Fluorosulfonate Which Do Not Fit the Hypothesis

Reactant	Registry no.	Intermediate cation(s)	Product
 11			
 30	142-08-5		
			
 33	108-96-3		
			

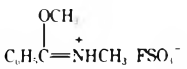
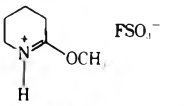
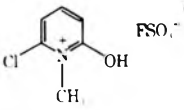
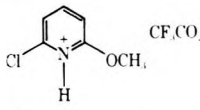
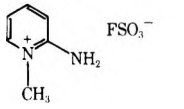
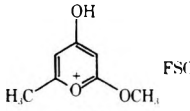
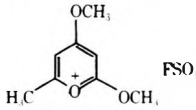
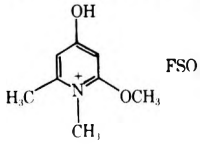
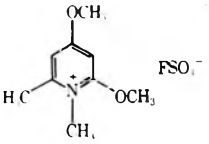
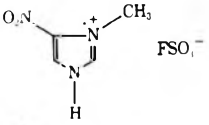
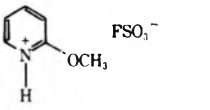
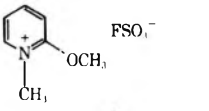
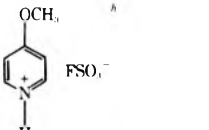
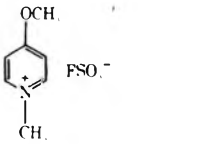
[a] The amide is the only product observed by NMR of the neutral products if the excess solvent and methyl fluorosulfonate are not removed prior to quenching with 1 N sodium hydroxide. [b] 2-Methoxypyridine and 1-methyl-2-pyridone are produced in 12 and 28% yields, respectively. [c] The reaction was carried out in neat methyl fluorosulfonate and quenched with aqueous base as soon as all the 4-pyridone had dissolved to give 4-methoxypyridine and 1-methyl-4-pyridone in 20 and 10% yields, respectively.

Table III. Methylation of 3-Chloro-2-pyridone with Methyl Fluorosulfonate in Methylene Chloride to Give 3-Chloro-2-methoxypyridine (28) and 3-Chloro-1-methyl-2-pyridone (29)

Reaction time, h	Excess methyl fluorosulfonate	Product, 28/29
3	Removed in vacuo	80/20
21[a]	Removed in vacuo	84/16
5	Not removed	46/54
0.1	Not removed	8/92
b	Not removed	5/95

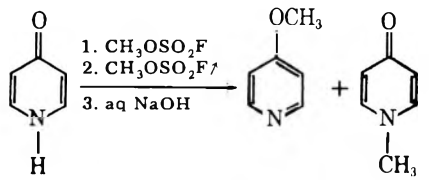
[a] Solvent was 5:3 benzene/methylene chloride; yield is 51%. [b] Reaction was carried out in the presence of 1 N aqueous KOH; yield was 92%.

Table IV. Proton Magnetic Resonance Spectra of Fluorosulfonate Salts

Compd	Registry no.	Chemical shifts,[a] δ
	65103-51-7	[b] 3.20 (d, NCH_3), 4.15 (OCH_3), 7.70 (C_6H_5)
	65103-52-8	2.70 (m, H_3 and H_6), 3.65 (m, H_4 and H_5), 4.16 (OCH_3)
	65103-54-9	8.00 (H_4), 7.25–7.50 (H_3 and H_5), 4.19 (NCH_3)
	65103-55-1	8.50 (H_4), 7.25–7.70 (H_3 and H_5), 4.26 (OCH_3)
	65103-56-2	[b] 7.00 and 7.80 (m, ArH), 3.75 (NCH_3)
	65103-58-4	[b] 6.86 (H_5), 6.55 (H_3), 4.23 (OCH_3), 2.59 (CCH_3)
	52911-90-7	[b] 6.96, 6.62 (H_3 and H_5), 4.17, 4.32 (OCH_3), 2.57 (CCH_3)
	65103-60-8	[b] 6.65, 6.72 (H_3 and H_5), 4.08 (OCH_3), 3.65 (NCH_3), 2.52 (CCH_3)
	65103-61-9	[b] 6.90, 6.72 (H_3 and H_5), 4.20, 4.05 (OCH_3), 3.70 (NCH_3), 2.40 (CCH_3)
	65103-63-1	8.75, 8.35 (H_2 and H_5), 4.35 (NCH_3)
	65103-64-2	8.1–7.3 (ArH), 4.30 (OCH_3)
	52911-95-2	8.1–7.3 (ArH), 4.38 (OCH_3), 4.09 (NCH_3)
	65103-65-3	8.30 (H_2 and H_6), 7.33 (H_3 and H_5), 4.25 (OCH_3)
	65103-66-4	8.50 (H_2 and H_6), 7.45 (H_3 and H_5), 4.20, 4.17 (OCH_3 and NCH_3)

[a] Relative to DDS in trifluoroacetic acid unless otherwise specified. [b] Relative to Me_4S; in acetonitrile-d_3. [c] Independently prepared by the reactions of 4-methoxy-6-methyl-2-pyrone and 2-methoxy-6-methyl-4-pyrone with methyl fluorosulfonate.[i] [d] Mp 126–128 °C. Anal. ($C_8H_{12}FNO_5S$) C, H, N. [e] Independently prepared by the reactions of 4-methoxy-1,6-dimethyl-2-pyridone and 2-methoxy-1,6-dimethyl-4-pyridone with methyl fluorosulfonate. [f] Essentially the same spectrum is obtained for 6-chloro-1-methyl-2-pyridone in trifluoroacetic acid. [g] The spectrum of 6-chloro-2-methoxypyridine in trifluoroacetic acid. [h] The same spectrum is obtained for 4-methoxypyridine in trifluoroacetic acid. [i] Prepared from 4-methoxypyridine and methyl fluorosulfonate.

favor of **32** at longer reaction times. Similar reaction of 4-pyridone (**33**) gives a mixture of 4-methoxypyridine (**34**) and 1-methyl-4-pyridone (**35**) in low yield.

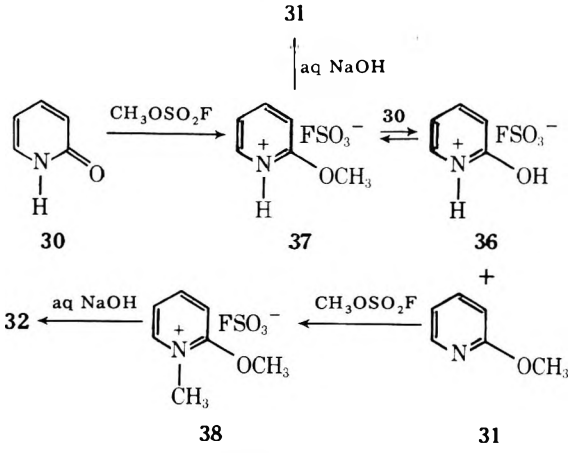


33 **34** **35**

The reaction of **30** has been investigated in detail. If the reaction is allowed to proceed overnight, a white solid precipitates which is 2-hydroxypyridinium fluorosulfonate (**36**). At shorter reaction times, the material obtained by evaporation of the excess methylfluorosulfonate is shown by proton magnetic resonance spectroscopy to be a mixture of 2-methoxypyridinium fluorosulfonate (**37**) and 2-methoxy-1-methylpyridinium fluorosulfonate (**38**). When the independently prepared fluorosulfonate salt **38** is treated with aqueous sodium hydroxide the only product is the pyridone **32**.[20]

These results can be accommodated by the process shown in Scheme II. It is proposed that after initial reaction of 2-pyridone (**30**) to give the expected salt **37** proton transfer to **30** occurs against an unfavorable equilibrium constant providing **36** and 2-methoxypyridine. The pyridine **31** then reacts with the methylating agent to give **38**, which gives 1-methyl-2-pyridone (**32**) on hydrolysis. The removal of **31** by methylation drives the reaction toward **36**, which eventually precipitates from the reaction medium. The formation of **36** explains the <50% yields. A decrease in **37** as a function of time would explain the variable ratio of **31** and **32**. The fact that 4-methoxypyridinium fluorosulfonate and 4-methoxy-1-

Scheme II



methylpyridinium fluorosulfonate can be isolated from the reaction of **33** with methyl fluorosulfonate suggests a similar course for that reaction. A large number of attempts to induce the reaction of 2-pyridone to yield only **37** by changes in solvent and methylating agent were not successful.[20]

The case of 2-pyridone shows that even though an initial reaction may follow the course prescribed by Figure 1a, that does not ensure synthetic success. In this case the site of initial methylation is obscured by subsequent events. The reaction of 2-pyridone suggests it may be difficult to achieve the synthetically prescribed regiospecific alkylation with protomeric ambident nucleophiles which are basic.

In an effort to extend the scope of these methylations, the reactions of thio acids, imides, β-hydroxy-α,β-unsaturated ketones, and β-amino crotonates with methyl fluorosulfonate were explored. In all cases mixtures of unidentified products were obtained. The cause of these difficulties was not determined, but the use of more reactive methylating agents should be explored.[12,21]

The present results raise interesting questions about the mechanism of alkylations of ambident protomeric nucleophiles. Questions about the nature of the actual nucleophile, the possible effects of association,[10] the possibility of proton or alkyl transfers of the salts,[22] and the relative transition-state energies for alkylation should be investigated.

In summary, the reaction profile of Figure 1a appears to be frequently observed for the reaction of protomeric ambident nucleophiles with methyl fluorosulfonate. For cases in which the initially formed salt is stable, it appears that isolation of the salt followed by treatment with base provides a regiospecific methylation in which the methyl group is bonded to the heteroatom remote from the proton in the major tautomer. On the other hand, complications with some cases suggest further efforts to stabilize the initially formed salts or to find more reactive alkylating agents would be useful.

Experimental Section

Caution: Methyl fluorosulfonate has been reported to be highly toxic; it should be used only with proper precautions.[23] Methyl fluorosulfonate (Aldrich) was purified by distillation from calcium hydride (bp 91–93 °C) and stored under nitrogen, over calcium hydride, at −15 °C prior to use.

2-Pyridone and 4-pyridone were purified by repetitive sublimations.[24] 2-Thiopyridone,[25] 4-thiopyridone,[25] 3-chloro-2-pyridone,[26] 4-hydroxy-6-methyl-2-pyridone,[27] 1,6-dimethyl-4-hydroxy-2-pyridone,[28] and *N*-methylthiobenzamide[29] were prepared by established methods and identified by their physical and spectral properties. All other reactants and solvents were commercially available and used without further purification.

General Procedure for Methylation. A five-to tenfold excess of methyl fluorosulfonate was added to the neat nucleophile or to a methylene chloride solution of the nucleophile. After being allowed to stir for 1–2 h at ambient temperature, any solid which formed was collected by filtration and the solution was heated in vacuo to remove solvent and excess methyl fluorosulfonate. The solid residue was examined by NMR spectroscopy in trifluoroacetic acid of acetonitrile-d_3 (Table IV).

Without further purification, the residue was treated with 1 N aqueous sodium hydroxide. The basic solution was extracted with either diethyl ether or chloroform and dried (Na_2SO_4), and the product isolated and purified by conventional methods. Products were identified by comparison of physical and spectral properties with established values: methylbenzimidic acid,[30] *N*-methyl methylbenzimidate,[31] *N*-phenyl methylacetimidate,[32] *N*-methyl methylbenzthioimidate,[33] *O*-methylvalerolactim,[22a] 2-methylthio-3,4,5,6-tetrahydropyridine,[9e] 6-chloro-1-methyl-2-pyridone,[34,35] 2-methylthiopyridine,[9e] 1-methyl-2-imidopyridone,[36] 2-methoxy-6-methyl-4-pyrone,[17] 4-methoxy-6-methyl-2-pyrone,[17] 2-methoxy-1,6-dimethyl-4-pyridone,[35] 4-methoxy-1,6-dimethyl-2-pyridone,[35] 1-methyl-5-nitroimidazole,[3] *N*-methylvalerolactam,[22a] 2-methoxypyridine,[22a] 1-methyl-2-pyridone,[22a] 4-methoxypyridine,[22a] 1-methyl-4-pyridone,[22a] 3-chloro-2-methoxypyridone,[26] 3-chloro-1-methyl-2-pyridone.[26]

The results of the methylations are presented in Tables I, II, and III.

Reaction of 2-Pyridone with Methyl Fluorosulfonate. To 2 mL of methyl fluorosulfonate was added 400 mg (4.2 mmol) of 2-pyridone. After being allowed to stir at ambient temperature for 5 min, the excess methylating agent was removed in vacuo and the residual solid was shown by comparison of its NMR spectrum (CF_3CO_2D) with that of authentic materials to be a mixture of 2-methoxypyridinium fluorosulfonate, 1-methyl-2-methoxypyridinium fluorosulfonate, and 2-hydroxypyridinium fluorosulfonate in a ratio of 24:30:36.

Separate treatment of the residue with 1 N aqueous sodium hydroxide followed by extractive separation of the products with chloroform and preparative thin-layer chromatography provided 2-methoxypyridine and 1-methyl-2-pyridone in 12 and 28% yields. Alternatively, if the hydrolysis of salts was carried out with neutral water followed by extraction with diethyl ether, 2-methoxypyridine free from 1-methyl-2-pyridine can be obtained in low yield.

2-Hydroxypyridinium Fluorosulfonate. Isolation on Methylation of 2-Pyridone. To 500 mg (5.2 mmol) of 2-pyridone suspended in 3 mL of methylene chloride was added 900 mg (10 mmol) of methyl fluorosulfonate. After being allowed to stir overnight, the white crystals collected by filtration were found to be a 10% yield of 2-hydroxypyridinium fluorosulfonate: mp 137–139 °C; NMR (CF_3CO_2D) δ 8.6–8.1 (m, 2 H), 7.6–7.3 (m, 2 H). Anal. ($C_5H_6FNO_4S$) C, H, N, S.

Reactions of 3-Chloro-2-pyridone with Methyl Fluorosulfonate. The reactions of 3-chloro-2-pyridone were carried out at ambient temperature with a four- to fivefold excess of methyl fluorosulfonate in methylene chloride for the time and with the disposition of excess methyl fluorosulfonate indicated in Table III. The reactions were worked up extractively. In an additional experiment, 0.3 mL (3.7 mmol) of methyl fluorosulfonate was added to 55 mg (0.44 mmol) of 3-chloro-2-pyridone in a mixture of 5 mL of methylene chloride and 7 mL of 1 N potassium hydroxide. After being allowed to stir for 21 h, extractive workup gave 60 mg of an oily product shown by NMR to be a 5:95 mixture of 3-chloro-2-methoxypyridine and 3-chloro-1-methyl-2-pyridone. 3-Chloro-2-methoxypyridine: δ 4.00 (s, 3 H), 6.81 (d of d, 1 H), 7.64 (d of d, 1 H), 8.09 (d of d, 1 H). 3-Chloro-1-methyl-2-pyridone: δ 3.60 (s, 3 H), 6.11 (t, 1 H), 7.29 (d of d, 1 H), 7.52 (d of d, 1 H).

Rate of Reaction of *N*-Methylbenzamide with Methyl Fluorosulfonate in Deuteriochloroform. The disappearance of the *N*-methyl signal of *N*-methylbenzamide and the appearance of the *O*-methyl signal of *O*-methyl-*N*-methylbenzamidic fluorosulfonate were followed in the NMR probe at ~38 °C. From two runs a second-order rate constant of 2.9 (±0.08) × 10^{-4} M^{-1} s^{-1} was obtained.

Acknowledgment. We are grateful to the National Institutes of Health—Institute of General Medicine and the National Science Foundation for support of this work.

Registry No.—Methyl fluorosulfonate, 421-20-5; 3-chloro-2-pyridone, 13466-35-8; 4-methoxy-6-methyl-2-pyrone, 672-89-9; 2-methoxy-6-methyl-4-pyrone, 4225-42-7; 4-methoxy-1,6-dimethyl-2-pyridone, 40334-97-2; 2-methoxy-1,6-dimethyl-4-pyridone, 40334-98-3; 6-chloro-1-methyl-2-pyridone, 17228-63-6; 6-chloro-2-methoxypyridine, 17228-64-7; 4-methoxypyridine, 620-08-6; 2-hydroxypyridinium fluorosulfonate, 65103-67-5; 3-chloro-2-methoxypyridine, 13472-84-9.

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Nucleophilic Aromatic Substitution on o-(Methoxy)aryloxazolines. A Convenient Synthesis of *o*-Alkyl-, o-Alkylidene-, and *o*-Arylbenzoic Acids

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Reaction of o-(methoxy)aryloxazolines **1** with organolithium or Grignard reagents results in methoxy displacement to the o-(alkyl)-, o-(aryl)-, and o-(vinyl)aryloxazolines **3**. A variety of organometallics were employed and only those considered to be delocalized anions failed to displace the methoxy group. Various poly(methoxy)aryloxazolines (**1a–e**) were investigated, and the reactions proceeded with general success, the yields dropping off in the 2,6-(dimethoxy)aryloxazoline **1d** due to steric factors. The method describes a facile synthesis of unsymmetrically substituted biphenyls and terphenyls by merely choosing the appropriate aryl metallic and methoxyaryloxazolines. Hydrolysis of the o-(substituted)aryloxazoline gave the corresponding benzoic acid derivatives **4** in good yield. In the case of 2,6-(disubstituted)aryloxazolines, hydrolysis to the benzoic acid proved difficult and led only to partially hydrolyzed amides.

Nucleophilic aromatic substitution has long been recognized as an important synthetic process, but has been limited to aromatic substrates with so-called "activating groups".[1] In recent years a number of elegant synthetic techniques have evolved which do not require the traditional activating groups and nucleophiles for substitution. Among these are the nickel-catalyzed reaction of aryl halides with Grignard reagents,[2] arene chromium derivatives reacting with carbanions,[3] the nickel-catalyzed reaction of enolates and aryl halides,[4] displacement on aryl halides[5] by alkoxide in powerful ion-solvating media, the copper-catalyzed substitution of o-bromobenzoic acids with enolates,[6] and the [2,3]sigmatropic rearrangements of sulfur ylides to ortho-substituted anilines.[7] The extensive studies by Bunnett,[8] which provided a variety of substituted benzenes, involve radical and radical ion intermediates and electron-transfer processes ($S_{RN}1$ mechanism). In effect, the overall transformation is that of nucleophilic substitution on aryl halides with traditional carbanions (enolates, thiolates, amide ions, etc.).

This report describes an aromatic substitution process which involves an activating group, but not in the traditional sense since it "activates" only toward nucleophilic reagents that are possessed of metal ions capable of chelation and transfer of the nucleophile from a tight ion pair to the electrophilic site.

In 1975, a preliminary report appeared[9] which described the overall process (eq 1) as a nucleophilic displacement of the o-methoxy group by several organometallics. This report will provide, in greater detail, the scope and limitations of this useful transformation and offer some evidence that the reaction is most probably occurring by an addition–elimination sequence and not by a free-radical mechanism.

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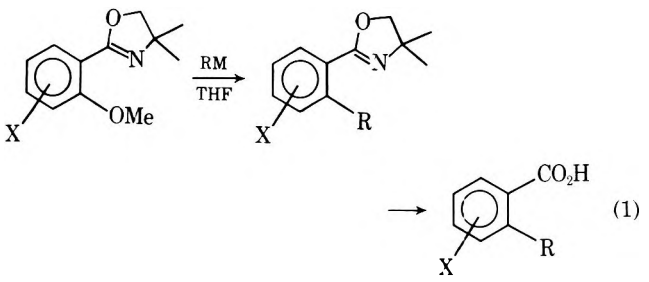
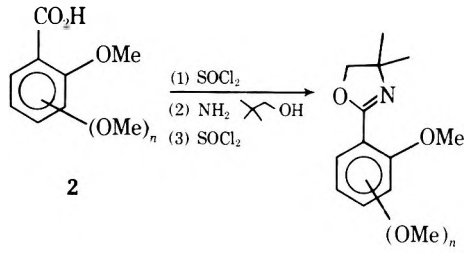


(1)

X = H, MeO; RM = alkyl or aryl lithium or Grignard

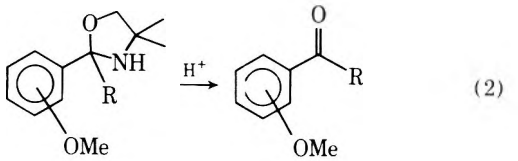
Since the appearance of the earlier report, a large number of examples have been investigated using five different methoxy-substituted aryloxazolines (**1a–e**) obtained in a simple



2 **1**

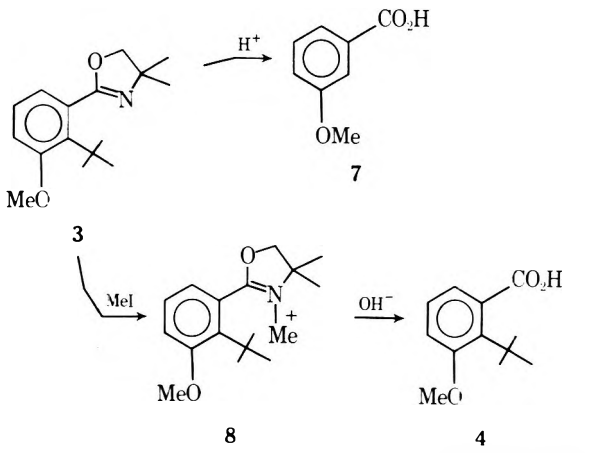
a, $n = 0$
b, $n = 1$ (3-methoxy)
c, $n = 1$ (4-methoxy)
d, $n = 1$ (6-methoxy)
e, $n = 2$ (4,5-dimethoxy)

transformation from the corresponding methoxy-substituted benzoic acids (**2**).[10] Reaction of these methoxyaryloxazolines with a wide variety of organometallic reagents led to ortho-substituted derivatives as outlined in eq 1 and tabulated in Table I. The treatment of **1** with organolithium reagents was performed at −30 to −45 °C and in many cases proceeded smoothly. At higher temperatures (>−20 °C) organolithium reagents added slowly to the C=N link of the oxazoline, leading to **5**. This was verified by hydrolysis to the ketones **6**



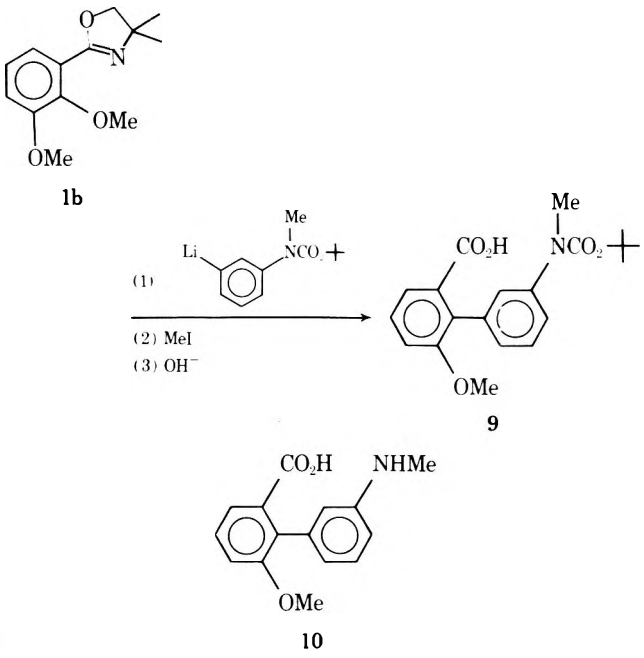
5 **6** (2)

(eq 2). For those cases (Table I, entries 1, 3, 18) where the methoxy displacement with organolithium was inefficient at −40 °C, the corresponding Grignard reagents were employed (entries 2, 4, 17) and gave excellent yields of products. The Grignard reagents could be introduced at 25 °C or, if necessary, heated without any addition to the oxazoline moiety. The resistance of 2-oxazolines to Grignard reagents and, hence, its use as a suitable protecting group have already been described.[10] The versatility of this process can be appreciated by examining the large variation in organometallic structures present in Table I. Prominent among these examples is the introduction of the *o-tert*-butyl group (entry 20) in high yield. However, removal of the oxazoline activating group under acidic conditions gave only *m*-methoxybenzoic acid **7**. The acid lability of the *tert*-butyl group in this instance could have valuable synthetic implications by selectively demethoxylating an *o*-methoxy group from an aromatic ring, a process without precedent. However, the *o-tert*-butylbenzoic acid **4** could be retrieved from **3** by conversion to the methiodide **8** and removal of the oxazolinium moiety by alkaline hydrolysis. Another example which took advantage of the alkaline removal of the oxazoline was that furnishing the biphenyl de-



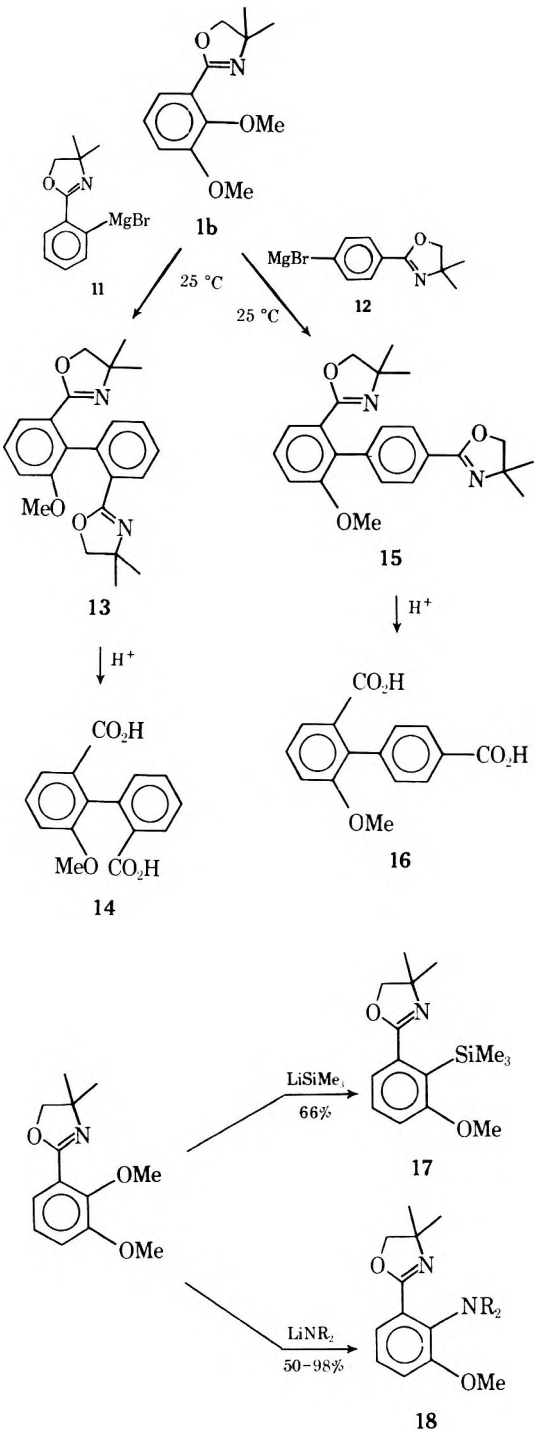
7 **3** **8** **4**

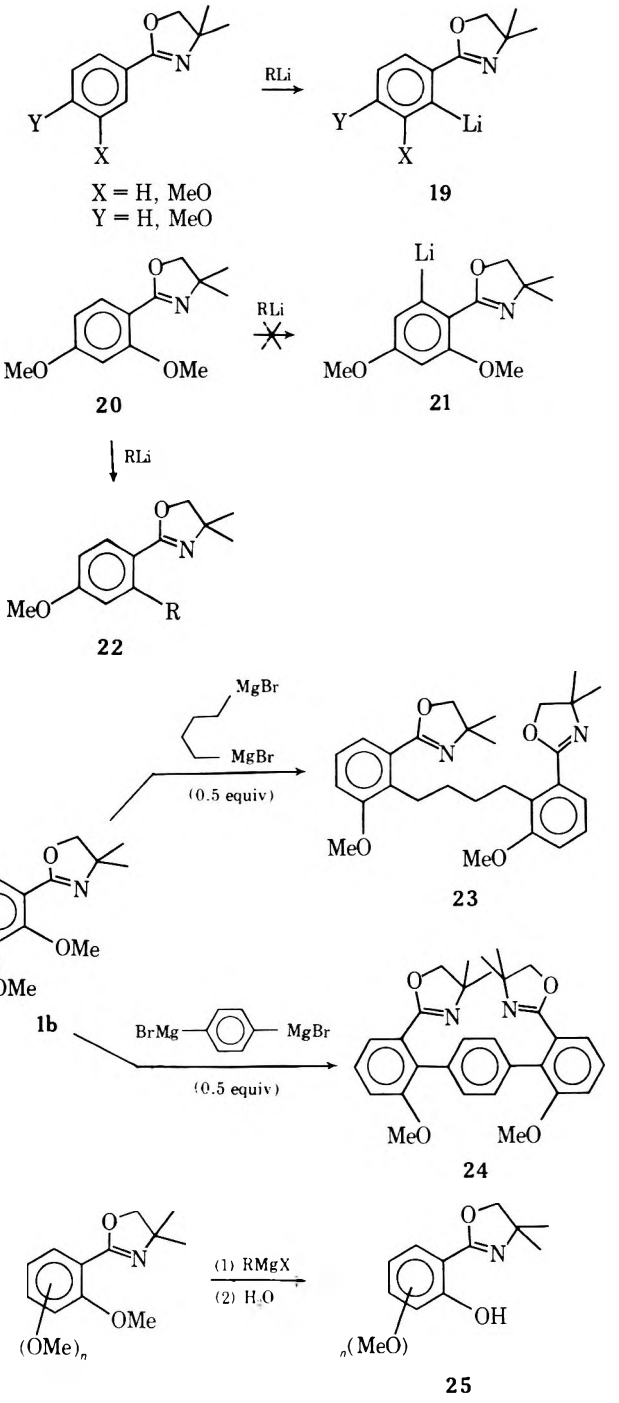
rivative **9** containing the acid sensitive Boc group. Whereas alkaline hydrolysis of the adduct gave **9** without event, acid hydrolysis led to the aminobiphenic acid **10**.



1b **9** **10**

The use of aryl metallics has proven to be a most convenient route to unsymmetrical biaryl derivatives, a synthetic challenge of long standing. Recent progress in biphenyl syntheses[2,11,12] has improved greatly on the classical Ullmann reaction,[13] but most suffer from chemospecificity and/or limitations leading only to symmetrical biaryls. Although several efficient biaryl preparations are listed in Table I (entries 4, 14–17, 25), an additional study was performed using both an electrophilic and a nucleophilic aryloxazoline. The conversion of *o*-bromobenzoic acid to its oxazoline and then its Grignard reagent **11** gave after treatment with **1b** an 88% yield of the biaryl **13**. Hydrolysis of **13** gave the unsymmetrical biphenic dicarboxylic acid **14** in 93% yield. Similar treatment of **1b** with the Grignard reagent **12** (from *p*-bromobenzoic acid) gave **15** (90%) and the isomeric biphenic acid **16** in 85% yield. This sequence illustrates the versatility of the oxazoline ring as an activating group in nucleophilic aromatic substitution as well as the ability of oxazolines to protect carboxyl functions toward Grignard formation. The process, by virtue of its nature, precludes any isomeric products and is truly a chemospecific route to biaryls containing a number of ortho substituents. Other metal derivatives also appear to behave similarly in this substitution process. Thus, lithiotrimethylsilane gave the o-(trimethylsilyl)aryloxazoline **17**, while a variety of lithioamines smoothly displaced the methoxy group, affording the o-amino derivatives **18**.[14] The facile introduction



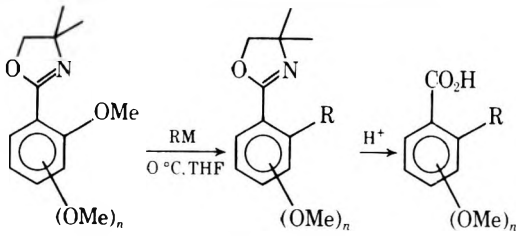


of the silyl group (**17**) provides a useful precursor for further substitution,[15] and a recent report by Dervan[16] has also opened new pathways for aryl silanes.

Metallation of aryloxazolines to **19** has been reported[17,18,19] to occur specifically ortho to the oxazoline activating group; however, if a methoxy group occupies an ortho position (**20**), no metallation occurs (to **21**) and only methoxy substitution takes place (**22**) (Table I, entries 21, 22). The absence of ortho lithiation was confirmed by quenching the reaction product of **20** with D_2O after addition of butyllithium (entry 22). In this instance undeuterated starting material was recovered in 51% yield. Grignard reagents derived from dihalides were also successfully employed, transforming **1b** into the 1,4-diarylbutane **23** and the terphenyl **24.** A general side reaction that was observed in these substitutions, particularly when Grignard reagents were employed, was the formation of the phenol **25** in 5–50% yields. The phenolic product, starting materials, and the substitution product were routinely separated using either column or preparative layer chromatography.

Introduction of organolithium reagents or Grignard reagents to the 2,6-(dimethoxy)aryloxazoline **1d** proceeded with less efficiency than the other aryloxazolines, presumably due to steric effects imparted by the two *o*-methoxyl groups (Table I, entries 23–25). For example, when 1 equiv of organometallic was added to **1d,** the substituted product **4** was isolated in moderate yield only after 40–90 h of reaction, thus indicating the slowness of the process. This may be attributed to the fact that the two *o*-methoxy substituents inhibit the oxazoline from achieving coplanarity with the aromatic nucleus. On the other hand, 2 equiv of phenyl Grignard reagent (after 76 h at 25 °C) gave a 93% yield of mono- and diarylated product **26** and **27** in equal amounts. An interesting facet of this reaction arose when it was found that the monoaryl product **26** when treated with phenyl Grignard reagent (excess, 126 h) gave no visible trace of the *m*-terphenyl derivative **27.** Thus, the biphenyl system (**26**) is not a precursor to the terphenyl system

Table I. Nucleophilic Substitution of 2-(o-Methoxyarl)oxazolines



1 3 4

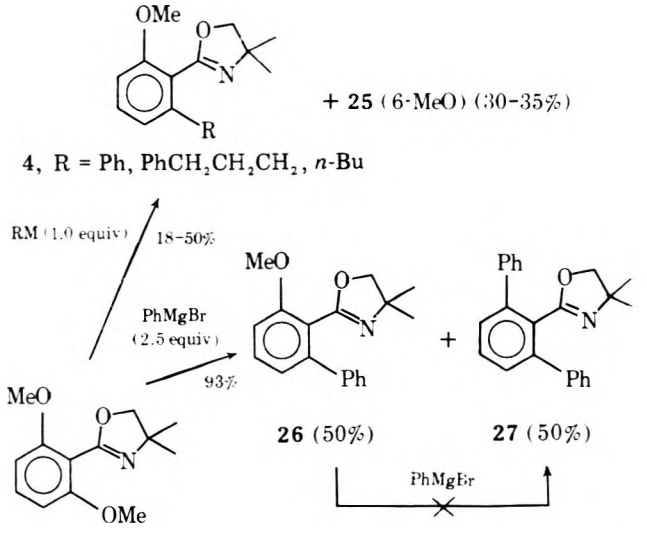
Entry	1	n	Posn	RM	Temp, °C	3,[a] %	Registry no.	4, %	Mp, °C	Registry no.
1	1a	0		n-BuLi	−35	22		74	39-40[b]	
2				n-BuMgBr	25	85				
3				PhLi	0	45		75	113-114[c]	
4				PhMgBr	25	95				
5	1b	1	3	n-BuLi	−45	98		93	101-102[d]	
6				MeMgBr	25	84		92	148-150[e]	
7				$Ph(CH_2)_2MgBr$	25	88		91	118-119[f]	65000-01-3
8				$Ph(CH_2)_3MgBr$	25	94		71	107-108[g]	64957-77-3
9				$PhCH_2MgBr$	25	6		h	69.0-69.5	
10				PhC≡CMgBr	25	31[i]	64957-79-5	67	146-148[j]	64957-78-4
11				CH_2=CHMgBr	25	66		90	125-127[k]	64957-80-8
12				CH_2=CHLi	−45	64				
13				(E)-PhCH=CHMgBr	25	61		87	128-130[l]	64957-81-9
14				4-(Ph)PhLi	−45	73		71	201-202[m]	57598-45-5
15				PhLi	−45	95		70	176-177[d]	
16				$4-(Me_2N)PhLi$	−45	66[n]	57598-37-5	69	253-254[o]	57598-46-6
17				2-(MeO)PhMgBr	25	95[p]	57598-39-7	78	196-197[q]	57598-49-9
18				2-(MeO)PhLi	−45	13				
19				EtLi	−45	88		75	120-121[r]	
20				t-BuLi	−45	95		45[t]	123-124[s]	57598-52-4
21	1c	1	4	EtMgBr	25	50[u]	64957-63-7			
22				n-BuLi	−22	47[v]	64957-64-8			
23	1d	1	6	n-BuLi[w]	−25	49[x]	64957-65-9			
24				$Ph(CH_2)_3MgBr$	25	18[y]	64957-66-0			
25				PhMgBr	25	50[z]	64957-67-1			
26	1e	2	4,5	n-BuMgBr	25	49		71	132-133[aa]	64957-69-3
27				EtMgBr	25	57[bb]	64957-68-2	h		

[a] Crude product unless otherwise noted. [b] C. D. Gutsche, G. L. Bachman, and R. S. Coffey, *Tetrahedron*, 18, 617 (1962). [c] "Handbook of Chemistry and Physics", 47th ed, The Chemical Rubber Co., Cleveland, Ohio. [d] H. Richtzenhain and P. Nippus, *Chem. Ber.*, 77, 566 (1944). [e] R. A. Barnes and R. W. Faessinger, *J. Org. Chem.*, 26, 4544 (1961). [f] Anal. Calcd: C, 74.98; H, 6.38. Found: C, 74.78; H, 6.31. [g] Anal. Calcd: C, 75.52; H, 6.72. Found: C, 75.48; H, 6.94. [h] Not hydrolyzed to benzoic acid derivative; melting point is that of the 2-benzyl derivative (registry no., 65000-00-2). Anal. Calcd: C, 77.26; H, 7.17. Found: C, 76.92; H, 6.94. [i] Reaction stirred at 25 °C for 7 days; mp 93.5-94.5 °C. [j] Anal. Calcd: C, 73.55; H, 5.02. Found: C, 73.21; H, 5.30 ($0.5H_2O$). [k] Anal. Calcd: C, 67.41; H, 5.66. Found: C, 67.55; H, 5.88. [l] Anal. Calcd: C, 75.57; H, 5.55. Found: C, 75.65; H, 5.61. [m] Anal. Calcd: C, 78.93; H, 5.30. Found: C, 78.88; H, 5.15. [n] Mp 110-110.5 °C. [o] Isolated as hydrochloride. Anal. Calcd: C, 62.44; H, 5.90. Found: C, 62.41; H, 5.77. [p] Mp 129-131 °C. Anal. Calcd: C, 70.07; H, 8.65. Found: C, 69.74; H, 8.79. [q] Anal. Calcd: C, 69.76; H, 5.46. Found: C, 69.46; H, 5.51. [r] H. Richtzenhain, *Chem. Ber.*, 77, 1 (1944). [s] Anal. Calcd: C, 69.21; H, 7.74. Found: C, 68.94; H, 8.00. [t] Hydrolysis performed on methiodide salt (Experimental Section). [u] Oil; bulb-to-bulb distillation at 55 °C (0.06 mm). Anal. Calcd: C, 72.07; H, 8.21. Found: C, 71.90; H, 8.06. [v] Oil; distilled at 60 °C (0.04 mm). Anal. Calcd: C, 73.53; H, 8.87. Found: C, 73.89; H, 9.04. [w] A 1.0-1.1 equiv amount of organometallic introduced. [x] Anal. Calcd: C, 73.53; H, 8.87. Found: C, 72.95; H, 8.72. [y] Oil; distilled bulb-to-bulb, 135 °C (0.05 mm). Anal. Calcd: C, 77.98; H, 7.79. Found: C, 77.85, H, 8.00. [z] Mp 95.0-95.5 °C. Anal. Calcd: C, 76.84; H, 6.81. Found: C, 77.05; H, 6.75. [aa] Anal. Calcd: C, 65.53; H, 7.61. Found: C, 66.00; H, 8.00. [bb] Oil; bulb-to-bulb distillation at 100 °C (0.05 mm). Anal. Calcd: C, 68.42; H, 8.04. Found: C, 68.82; H, 8.26.

(27). This is not surprising in view of the large ortho substituents present in **26**. Thus, the terphenyl system must have arisen from some intermediate during the reaction.

If it is assumed that these reactions proceed via an addition–elimination sequence (Scheme I), then the σ complex B allows the oxazoline to align itself in a coplanar fashion with the aromatic ring while the metal (Mg^{2+} or Li^+) forms a strong complex with the methoxy group. The transition state leading to B may be envisioned as forming from A, where the R group of the organometallic enters from the side almost perpendicular to the aromatic ring (to the π cloud). This is consistent with the lack of steric inhibition to addition by large groups (*tert*-butyl, phenyl, etc.). However, if there are two ortho substituents, complex A and ultimately B become difficult to form and the reaction is slow or unable to occur. Thus, the failure of **26** to form the terphenyl **27** is understandable.

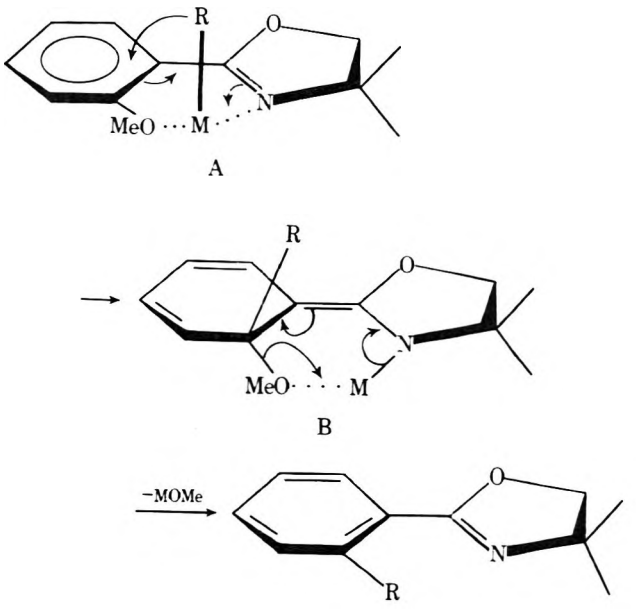
However, if the second phenyl group enters after the initial phenyl group is still in the σ complex C (Scheme II), complexation of phenyllithium may occur to the oxazoline sandwiched between the initial phenyl and methoxy group and addition may ensue with expulsion of the 2-methoxyl group. In effect, the second phenyl is introduced in a 1,8 addition to C. The relative rates of addition (C, k_2) and elimination (**26**, k_1) therefore determine the 1:1 mixture which results.[23] In those instances where 2,6-(disubstituted)aryloxazolines are formed, hydrolysis to the benzoic acids by removal of the ox-



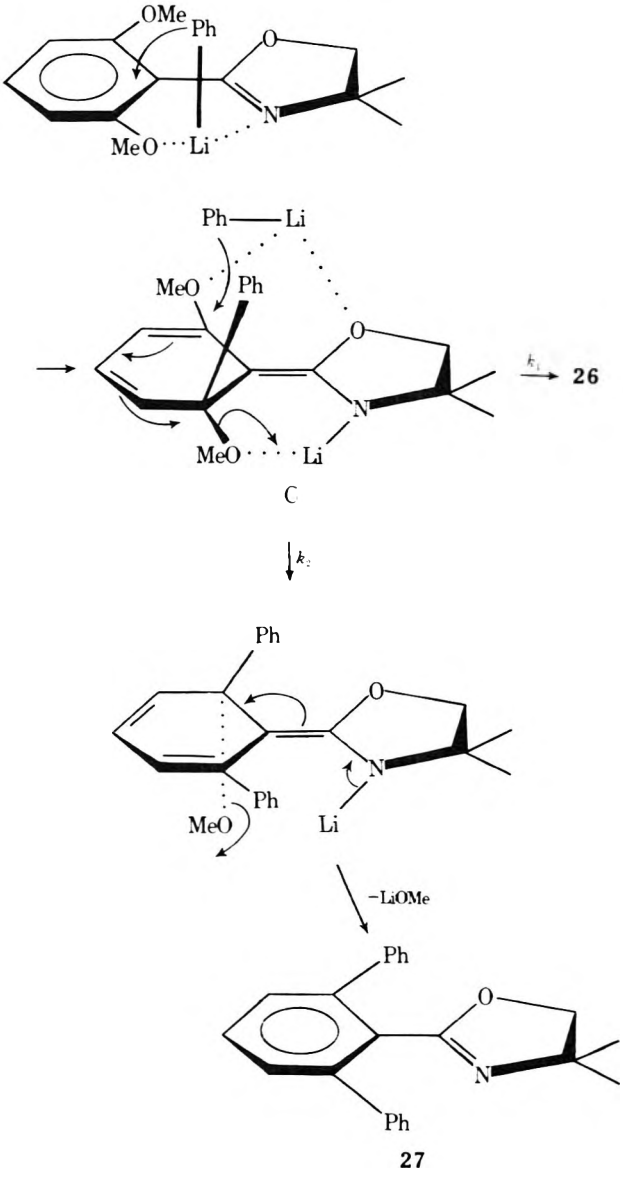
azoline has thus far proved to be unsatisfactory. The usual steric effects toward hydrolysis are obviously in play, and further efforts in this regard are in progress.

The importance of organometallic (RM) complexation to the *o*-(methoxy)aryloxazolines **1** (A in Scheme I) cannot be overstated since a number of organometallic reagents failed to substitute the methoxy group. Grignard and lithium reagents which gave no substitution are listed in Table II. Benzyl Grignard reagent gave 5–6% of the substitution products, but all of the others listed gave only starting material or demethylation (10–50%) to the phenol **25.** A glance at the structures in Table II indicates that all are delocalized or intramolecularly chelated anions. It would therefore seem that failure to add to the aromatic ring is due to (a) the complex A generating an anion sufficiently delocalized to allow its addition or (b) the intramolecular complexation already present in the organometallic precluding any complexation with the methoxyaryloxazoline. For lithium ethanethiolate, the high nucleophilicity of the sulfur results in rapid and complete demethylation of the *o*-methoxy group, affording **25** in quantitative yield. The failure of LiSEt to displace methoxy also enhanced the assumption that the substitution reactions were not occurring by an electron-transfer (ET) process since sulfides are known to be excellent ET reagents.[20] In order to assess further the possibility of an ET mechanism

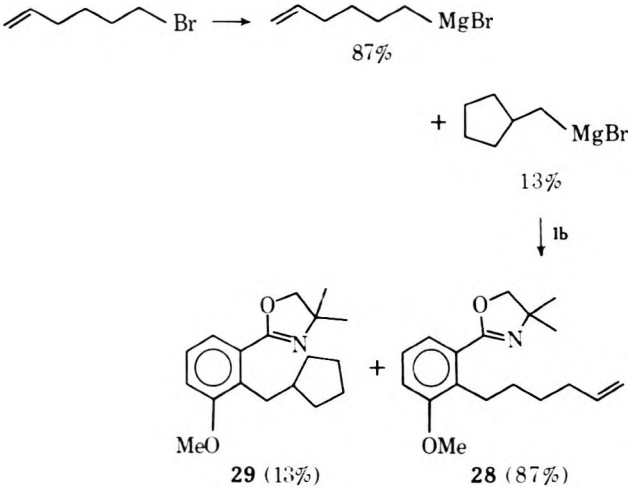
Scheme I



Scheme II



for this reaction, 1-bromohexene and its Grignard reagent were examined as an alkylating agent. It is well-known[21] that hexenylmagnesium bromide in a radical reaction rearranges rapidly ($k_{cycln} = 10^5\ s^{-1}$) to cyclopentylmethylmagnesium bromide. Therefore, reaction with **1b** should give a large amount of **29** as a byproduct in the formation of **28** if alkyla-



tion proceeded by an ET route. Hexenyl bromide was transformed[22] into its Grignard reagent (THF), and prior to reaction with **1b** it was quenched and analyzed (VPC) for the ratios of *n*-hexene and methylcyclopentane. The ratio of several runs was 87 ± 3% of the former and 13 ± 3% of the latter, in agreement with the literature.[22] Reaction with **1b** gave **28** and **29** in 73% yield, and NMR analysis indicated that 87% of **28** and 13% of **29** was present. Thus, there was virtually no change in the composition of the products compared to the composition of the starting Grignard reagents. It therefore may be concluded that if the alkylation of methoxyaryloxazoline is an ET process, its rate constant must be considerably faster than 10^5 s^{-1}, the rate constant for the rearrangement of hexenyl to cyclopentylmethyl radical. In view of the efficiency of lithioamides[14] in this reaction and the unlikelihood of their ability to proceed by ET mechanisms, it can be assumed at this time that this highly useful synthetic process is occurring through an addition–elimination sequence.

Further studies on polynuclear aromatics and heteroaromatics are in progress, and results of these efforts will be reported in due course.

Experimental Section

2-(2-Methoxyphenyl)-4,4-dimethyl-2-oxazoline (1a). A mixture of 50 g (330 mmol) of *o*-anisic acid and 117.3 g (980 mmol) of thionyl chloride was stirred at 25 °C for 24 h. The excess thionyl chloride was removed in vacuo, and the residue was distilled (bp 68 °C, 0.05 mm), yielding 51.4 g of the acid chloride as a colorless oil. A solution of the acid chloride in 75 mL of methylene chloride was added dropwise to 53.7 g (600 mmol) of 2-amino-2-methyl-1-propanol in 125 mL of methylene chloride at 0 °C. After stirring for 2.5 h at 25 °C, the solution was filtered and the filtrate evaporated to give 68.3 g of the crystalline amide. The latter (25 g) was treated dropwise with 40.2 g of thionyl chloride and magnetically stirred. The solution was then poured into 150 mL of dry ether, and the oxazoline hydrochloride precipitated and was removed by filtration. The salt was neutralized with 20% sodium hydroxide, and the alkaline solution was extracted with ether, dried ($MgSO_4$), and concentrated to give an oil (21 g, 83%), which crystallized on standing, mp 66–68 °C. An analytical sample was purified by recrystallization from hexane, mp 68–69.5 °C; IR (KBr) 1635 cm^{-1}; NMR (CCl_4) δ 7.75 (m, 1), 7.33 (m, 1), 6.94 (m, 2), 3.96 (s, 2), 3.86 (s, 3), 1.33 (s, 6).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.47; H, 7.47.

2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1b). In a manner similar to the preparation of **1a**, 12 g of 2,3-dimethoxybenzoic acid gave 10.44 g (70%) of **1b**, mp 49–50 °C; IR (film) 1642 cm^{-1}; NMR (CCl_4) δ 6.8–7.4 (m, 3), 3.96 (s, 2), 3.85 (s, 3), 3.78 (s, 3), 1.33 (s, 6).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.31; H, 7.54.

2-(2,4-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1c). Following the procedure for **1a**, 50 g of 2,4-dimethoxybenzoic acid gave 35.2 g (56%) of **1c** as a viscous oil, which was purified by chromatography (silica gel) using ethyl acetate as the eluent; IR (film) 1630 cm^{-1}; NMR (CCl_4) δ 7.57 (d, J = 9 Hz, 1), 6.32 (md, 2), 3.85 (s, 2), 3.73 (s, 3), 3.68 (s, 3), 1.27 (s, 6).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.12; H, 7.12.

2-(2,6-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1d). Following the procedure for **1a**, 25.0 g of 2,6-dimethoxybenzoic acid gave 24.5 g (76% overall) of **1d**, mp 64–65 °C (hexane); IR (film) 1665 cm^{-1}; NMR (CCl_4) δ 7.22 (t, J = 9 Hz, 1), 6.50 (d, J = 9 Hz, 2), 3.93 (s, 2), 3.77 (s, 6), 1.33 (s, 6).

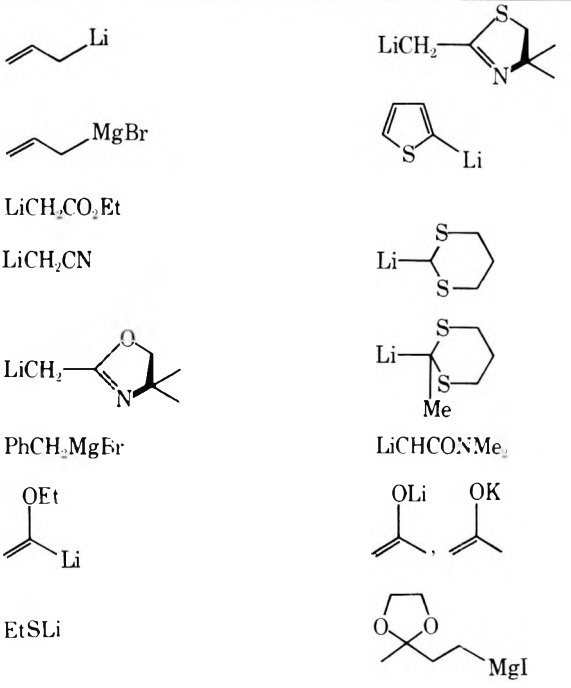
Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.42; H, 7.04.

2-(2,4,5-Trimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1e). This compound was prepared in 60% overall yield from 10 g of 2,4,5-trimethoxybenzoic acid according to the procedure given for **1a**, mp 84–86 °C (hexane); IR (film) 1630 cm^{-1}; NMR (CCl_4) δ 7.27 (s, 1), 6.40 (s, 1), 3.93 (s, 2), 3.82 (s, 6), 3.78 (s, 3), 1.33 (s, 6).

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.47; H, 7.34.

Reaction of 1 (a–e) with Organolithium Reagents. General Procedure. The formation of compounds **3** in Table I using organolithium reagents was accomplished using the following procedure for all. A solution of **1** (**a–e**), 14.5 mmol, in 60 mL of THF was cooled to −45 °C under a nitrogen atmosphere. To this was added dropwise 15.5–16.0 mmol of organolithium reagent in the appropriate solvent (hexane, ether, or THF). In some cases the addition of organolithium reagent was accompanied by an exotherm (usually alkyllithium), and the reaction was held below −35 °C by adjusting the rate of addition. Stirring of the resulting amber solution at −30 °C was continued until TLC monitoring (ethyl acetate–hexane) indicated the absence of starting material (usually 1–3 h). In most instances the reaction was allowed to slowly warm to 0 °C and quenched in saturated ammonium chloride solution, extracted (3 times) with ether, dried (K_2CO_3), and concentrated. The products were purified by preparative thin-layer or column chromatography on silica gel (ethyl acetate–hexane). In other cases the product was distilled, bulb-to-bulb, under a vacuum.

Table II. Organometallics Failing to React with *o*-(Methoxy)aryloxazolines



Reaction of 1 (a–e) with Grignard Reagents. General Procedure. The formation of **3** in Table I using Grignard reagents was performed as follows. The Grignard reagent (6.00 mmol) in ether or THF was slowly added to 5.8 mmol of **1** (**a–e**) in 10 mL of THF under argon or nitrogen at 25 °C. Stirring of the solution was usually performed for 16–20 h or longer if TLC monitoring (silica gel, ethyl acetate–hexane) indicated the presence of starting material. Workup of the reaction mixture as described above gave the crude product, which was purified by bulb-to-bulb distillation and column or preparative thin-layer chromatography (silica gel, ethyl acetate–hexane).

Hydrolysis of Oxazolines 3 to Benzoic Acids 4. General Procedure. The oxazolines (5 mmol) were dissolved in 100 mL of 4.5 N hydrochloric acid and heated to reflux for 16–24 h. After cooling, the heterogeneous mixture was extracted with ether (3 times). The ethereal extracts were washed with water and saturated brine, dried ($MgSO_4$), and concentrated to give products of acceptable purity. Further purification was achieved by recrystallization from hexane, ethanol–water, or water, depending on the solubility properties.

2-Methoxyvalerophenone from 5 (2-MeO; R = *n*-Bu). In a typical experiment, 2 mL (5.0 mmol) of 2.5 M *n*-BuLi in hexane was added slowly to 1.03 g (5.0 mmol) of **1a** in THF at −35 °C. The solution was stirred for 3 h and then warmed to ambient temperature. The usual aqueous workup afforded 22% of **3** (R = *n*-Bu; *n* = 0) and 49% of **5** after preparative TLC (silica gel, 20% ethyl acetate–hexane). Hydrolysis of **5** in 4.5 M hydrochloric acid for 18 h at reflux gave the crude ketone, purified by elution through silica gel with 10% acetone–hexane; IR (film) 1680, 1025 cm^{-1}; NMR (CCl_4) δ 6.75–7.73 (m, 4), 3.87 (s, 3), 2.90 (t, J = 7 Hz, 2), 1.13–1.93 (m, 4), 0.68–1.12 (m, 3).

Anal. Calcd: C, 74.97; H, 8.39. Found: C, 74.87; H, 8.12.

The 2,4-DNP melted at 126.4–126.6 °C (from ethanol).

Reaction of 1b with *tert*-Butyllithium. 2-*tert*-Butyl-3-methoxybenzoic Acid 4 (3-MeO; R = *t*-Bu). In a manner using the

general procedure for organolithium reagents, 0.380 g (1.62 mmol) of **1b** in 40 mL of THF and 1.4 mL (3.22 mmol) of 2.3 M *tert*-butyllithium gave 0.427 g (~99%) of **3** (R = *t*-Bu; 3-MeO) as a clear oil; IR (CCl_4) 1665 cm^{-1}; NMR (CCl_4) δ 7.3–6.6 (m, 3), 3.93 (s, 2), 3.85 (s, 3), 1.48 (s, 9), 1.33 (s, 6).

Without further purification, 3 was stirred with excess methyl iodide at room temperature overnight and the excess methyl iodide removed in vacuo. To the crude methiodide salt was added 12 mL of methanol and 12 mL of 20% aqueous sodium hydroxide, and the mixture was heated to reflux for 12 h. The solution was extracted with ether and the ethereal extracts were discarded. The aqueous solution was neutralized to pH 2 (9 N HCl), extracted with ether, dried ($MgSO_4$), and concentrated to afford **4**. Recrystallization from hexane provided pure 2-*tert*-butyl-3-methoxybenzoic acid (45%), mp 123–124 °C; IR (CCl_4) 1695 cm^{-1}; NMR (CCl_4) δ 11.9 (s, 1), 7.33–6.75 (m, 3), 3.86 (s, 3), 1.53 (s, 9).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.94; H, 8.00.

2-Carboxy-6-methoxy-3′-(*N*-methyl-*N*-*tert*-butoxycarbonyl)biphenyl (9). 3-Bromo(*N*-methyl-*N*-Boc)aniline (0.472 g) was converted to its lithio salt by addition of 0.72 mL of 2.3 M *n*-butyllithium (hexane) to a THF solution at −78 °C. After 15 min, the solution was warmed to −45 °C and 0.353 g of **1b** in 15 mL of THF was added. The solution was stirred for 5 h at −45 °C and then warmed to 25 °C, quenched in ammonium chloride (saturated), extracted with ether, dried, and concentrated. Chromatography, as above, afforded the biaryloxazoline, mp 93–97 °C. Without further purification the latter was hydrolyzed in two fashions.

(A) Acidic Hydrolysis to 10. A solution of the above (0.2 mmol) in 10 mL of 4 N hydrochloric acid was heated to reflux (12 h). Ether extraction gave no ether-soluble material. The pH was adjusted to 6 with saturated sodium bicarbonate. Ether extraction produced crude **10** (40%). Conversion to its hydrochloride (dry HCl passed into an ethereal solution of **10**) gave mp 200 °C dec; IR (KBr) 1695 cm^{-1}; NMR (Me_2SO-d_6) δ 8.7 (brd s, 2), 7.8–7.0 (m, 7), 3.73 (s, 3), 3.13 (s, 3).

Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49. Found: C, 61.11; H, 5.78.

(B) Alkaline Hydrolysis to 9. The biaryloxazoline was stirred in the presence of a 5-fold excess of methyl iodide overnight and the excess methyl iodide removed in vacuo. To the crude methiodide (0.097 g) was added 25 mL of a 1:1 solution of methanol and 20% sodium hydroxide, and the mixture was heated to reflux for 15 h. Cooling was followed by ether extraction, and the latter phase was discarded. Acidification of the aqueous phase to pH 2 (9 N HCl) and ether extraction, drying ($MgSO_4$), and concentration gave 0.05 g (65%) of **9** as a colorless solid, mp 52–55 °C (hexane); IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 7.85 (s, 1), 7.65–6.70 (m, 7), 3.72 (s, 3), 3.22 (s, 3), 1.42 (s, 9).

Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 67.43; H, 6.26.

2,4′-(Dicarboxy)-6-methoxybiphenyl (16). The preparation of the *p*-(magnesiobromide)phenyloxazoline **12** has been reported.[10] The deep red Grignard reagent was added to 1.18 g (5 mmol) of **1b** in 10 mL of THF at 25 °C. After stirring for 15 h, the solution was worked up in the usual way to give 2.11 g of a yellow solid, **15**. Purification via preparative TLC (50% ethyl acetate–hexane) gave 1.71 g, mp 151–153 °C (90%). Spectral characteristics for **15** were the following: IR (film) 1645, 1045 cm^{-1}; NMR (CCl_4) δ 6.67–8.07 (m, 7), 4.03 (s, 2), 3.67 (s, 3), 3.60 (s, 2), 1.35 (s, 6), 1.15 (s, 6).

The biaryloxazoline **15** was hydrolyzed by heating to reflux 0.75 g in 4.5 N HCl for 18 h. The resulting solid was filtered and recrystallized from ethanol–water to give 0.462 g (85%) of **16** as a colorless solid, mp 224–227 °C; IR (KBr) 2300–2400, 1675, 1050 cm^{-1}; NMR (Me_2SO-d_6) δ 11.7–12.7 (brd s, 2), 7.10–8.23 (m, 7), 3.72 (s, 3).

Anal. Calcd: C, 66.17; H, 4.45. Found: C, 66.01; H, 4.31.

2,2′-(Dicarboxy)-6-methoxybiphenyl (14). In a fashion similar to **16** above, 1.79 g of *o*-bromophenyloxazoline was converted to its Grignard reagent[10] and added to 1.18 g of **1b** in 10 mL of THF. The solution was stirred at 25 °C for 60 h and then poured into saturated ammonium chloride, extracted with ether, dried (K_2CO_3), and concentrated to give 2.25 g of crude **13**. Purification on silica gel using preparative TLC (50% ethyl acetate–hexane) gave 1.66 g (88%) of pure **13**, mp 99–101 °C; IR (film) 1650, 1040 cm^{-1}; NMR (CCl_4) δ 6.70–8.00 (m, 7), 3.57–3.67 (s, 7), 0.88–1.27 (s, 12).

Hydrolysis was performed by heating 0.756 g of **13** in 4.5 N HCl for 24 h. The solid was collected by filtration and recrystallized from water to give 0.467 g (93%) of pure **14**, mp 222–224 °C; IR (film) 2300–3500 broad, 1680, 1060, cm^{-1}; NMR (Me_2SO-d_6) δ 11.67–12.77 (brd, 2), 6.67–8.43 (m, 5), 3.67 (s, 3).

Anal. Calcd: C, 66.17; H, 4.45. Found: C, 66.27; H, 4.35.

2-(3-Methoxy-2-trimethylsilylphenyl)-4,4-dimethyl-2-oxazoline (17). Methyllithium (3.8 mL, 1.45 M) was added to 1.2 mL (6.0 mmol) of hexamethyldisilane in 4 mL of dry HMPA at 0 °C. After stirring for 20 min, 10 mL of dry THF was added and the solution was cooled to −78 °C. A solution of 1.18 g (5 mmol) of **1b** in 5 mL of THF was introduced, and the deep red mixture was stirred for 2 h at −78 °C and then warmed to 0 °C over 1 h. The usual workup gave crude **17**, which was purified by preparative thin-layer chromatography (50% ethyl acetate–hexane), furnishing 58 mg of **1b** and 0.907 g of **17** as an oil. Distillation, bulb-to-bulb, at 70 °C (0.05 mm) gave pure material (66%); NMR (CCl_4) δ 6.67–7.38 (m, 3), 3.95 (s, 2), 3.73 (s, 3), 1.32 (s, 6), 0.30 (s, 9).

Anal. Calcd: C, 64.94; H, 8.36. Found: C, 65.15; H, 7.89.

1,4-Bis(2-oxazinyl-6-methoxyphenyl)butane (23). 1,4-Dibromobutane (0.54 g, 2.5 mmol) was added to 0.243 g of magnesium turnings in 10 mL of dry THF. The resulting Grignard reagent was then added to 1.18 g (5.0 mmol) of **1b** in 5 mL of THF at 25 °C. The solution was stirred at room temperature for 21 h and then heated at reflux for 24 h. The usual workup gave the crude product, which was purified by preparative TLC (silica gel, 50% ethyl acetate–hexane) to give 0.320 g of **25** (3-MeO) and 0.333 g (29%) of **23** as a colorless solid, mp 150–151 °C (hexane); NMR ($CDCl_3$) δ 6.73–7.43 (m, 6), 4.05 (m, 4), 3.82 (m, 6), 2.77 (m, 4), 1.17–1.80 (m, 4), 1.40 (s, 12).

Anal. Calcd: C, 72.39; H, 7.81. Found: C, 72.43; H, 7.95.

1,4-Bis(2-oxazinyl-6-methoxyphenyl)benzene (24). A mixture of 1.18 g of **1b**, 0.170 g of magnesium turnings, and 0.590 g of *p*-dibromobenzene in 15 mL of dry THF was heated under reflux for 24 h. The standard workup gave the crude product, which was purified by preparative TLC (silica gel, 50% ethyl acetate–hexane, eluted twice). There was cut (ether) from the plate 0.116 g of **25** (11%), 0.284 g of **3** (Table I, entry 15; 20% yield), and 0.365 g (30%) of **24**. Recrystallization from ethyl acetate–hexane gave pure **24**, mp 220–221 °C; NMR (CCl_4) δ 6.90–7.47 (m, 10), 3.77 (s, 3), 3.75 (s, 4), 1.27 (s, 12).

Anal. Calcd: C, 74.36; H, 6.66. Found: C, 74.17; H, 6.59.

2-(2,6-Diphenylphenyl)-4,4-dimethyl-2-oxazoline (27). A solution of 1.18 g (5.0 mmol) of **1b** in 5 mL of THF was treated with 12.5 mmol of phenylmagnesium bromide (from 1.96 g of bromobenzene and 0.30 g of magnesium turnings in 17 ml of THF), and the mixture was stirred for 76 h at room temperature. After quenching (saturated NH_4Cl), ether extraction, drying (K_2CO_3), and concentration, the crude mixture was purified by preparative TLC (silica gel, 50% ethyl acetate–hexane). The faster moving band was cut away and extracted with ether to give, after evaporation, 0.70 g (50%) of **27**, mp 96.5–97.5 °C; IR (film) 1660, 1456, 1038, 760, 700 cm^{-1}; NMR (CCl_4) δ 6.27–7.60 (m, 13), 3.47 (s, 2), 0.87 (s, 6).

Anal. Calcd: C, 84.37; H, 6.46. Found: C, 84.65; H, 6.59.

The slower moving band, after similar isolation, gave 0.699 g (49.8%) of **26** (Table I, entry 25). Treatment of **26** with 2.0 equiv of phenylmagnesium bromide in THF for 170 h gave complete recovery of the starting material.

Reaction of 1b with 5-Hexenylmagnesium Bromide. Preparation of 28 and 29. Freshly distilled 6-bromo-1-hexene (1.06 g, 6.50 mmol) was added to 0.160 g of magnesium turnings in 10 mL of dry THF. After the Grignard reagent was completely formed, 0.25 mL was withdrawn and quenched in water. Analysis by VPC indicated 87–90% of 1-hexene and 10–13% of methylcyclopentane. The remainder of the Grignard reagent was added to 1.18 g of **1b** in 7 mL of THF at 25 °C and stirred for 6 h. Standard workup gave 1.46 g of an oil, which was purified to remove starting material (**1b**, 8%) by preparative TLC (50% ethyl acetate–hexane). The overlapping bands were removed together from the silica gel with ether and evaporated to leave 1.08 g of a mixture of **28** and **29**. NMR analysis indicated that the mixture consisted of 87% of **28** and 13% of **29**. Analysis of the mixture gave the following results: NMR (CCl_4) δ 6.67–7.43 (m, 3), 4.77–6.00 [m, vinyl region, 2.5 (87%)], 3.92 (s, 2), 3.75 (s, 3), 2.80–3.23 (m, 2), 1.87–2.33 (m, 2), 1.40–1.77 (m, 4), 1.32 (s, 6).

Anal. Calcd: C, 75.22; H, 8.77. Found: C, 74.91; H, 8.79.

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Registry No.—**1a**, 57598-33-1; **1a** (HCl), 64957-82-0; **1b**, 57598-32-0; **1b** (HCl), 64957-83-1; **1c**, 64957-84-2; **1c** (HCl), 64957-85-3; **1d**, 64957-86-4; **1d** (HCl), 64957-87-5; **1e**, 64957-88-6; **1e** (HCl), 64957-89-7; **2a**, 579-75-9; **2a** (acid chloride), 21615-34-9; **2b**, 1521-38-6; **2b** (acid chloride), 7169-06-4; **2c**, 91-52-1; **2c** (acid chloride), 39828-35-8; **2d**, 1466-76-8; **2d** (acid chloride), 1989-53-3; **2e**, 490-64-2; **2e** (acid

chloride), 42833-66-9; **3** (R = Bu; n = 0), 57629-47-7; **3** (R = t-Bu; 3-MeO), 57598-43-3; **3** (R = t-Bu; 3-MeO) methiodide, 65000-02-4; **4** (R = t-Bu; 3-MeO), 57598-52-4; **5** (R = Bu; 2-MeO), 64957-90-0; **6** (R = Bu; 2-MeO), 20359-54-0; **9**, 57598-48-8; **10** (HCl), 64957-91-1; **13**, 64957-92-2; **13** (meta analogue), 64957-93-3; **14**, 38197-35-2; **15**, 64957-94-4; **16**, 64957-71-7; **17**, 64957-72-8; **23**, 64957-73-9; **24**, 65000-03-5; **27**, 64957-74-0; **28**, 64957-75-1; **29**, 64957-76-2; thionyl chloride, 7719-09-7; 2-amino-2-methyl-1-propanol, 124-68-5; 3-bromo(N-methyl-N-Boc)aniline, 57598-34-2; 2-p-bromophenyl-4,4-dimethyloxazol-2-ine, 32664-14-5; 2-o-bromophenyl-4,4-dimethyloxazol-2-ine, 32664-13-4; hexamethyldisilane, 1450-14-2; 1,4-dibromobutane, 110-52-1; p-dibromobenzene, 106-37-6; bromobenzene, 108-86-1; 6-bromo-1-hexene, 2695-47-8; 2-methoxyvalerophenone 2,4-DNP, 64957-70-6.

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(23) Professor D. J. Cram (UCLA) informed us that the addition of a large excess of phenylmagnesium bromide to **1d** gave the m-terphenyl derivative **27** in quantitative yield.

Sulfenylation and Sulfinylation of Lactams and Imino Ethers

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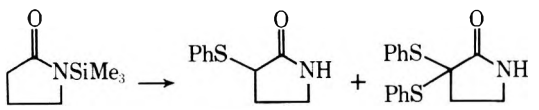
The sulfenylation of 1-trimethylsilyl-2-pyrrolidinone (**1**) with phenyl disulfide under a variety of reaction conditions afforded the bissulfide **3** as the major product along with the monosulfide **2**. The direct sulfinylation of **1** with methyl benzenesulfinate, however, could be achieved to afford the sulfoxide **4**. An analogous sulfinylation of 1-methyl-2-pyrrolidinone gave the sulfoxide **13** in excellent yield. The imino ether **5** could be monosulfenylated effectively by employing a 1:2:1 ratio of lactam/base/electrophile. It was also observed that in the sulfenylation of the N-alkyllactams **7** and **8** that HMPA had no effect on promoting bissulfenylation and that the ratio of substrate/base/electrophile is very important.

Recently, we reported[2] that mono- or bissulfenylation or selenenylation of N-methyllactams can be cleanly controlled by varying the equivalents of base utilized in the reaction. It has also been demonstrated[3] that an α-phenylselenenyl or an α-phenylsulfenyl moiety can be used to introduce a $\Delta^{3,4}$ double bond in an intact 2-pyrrolidinone nucleus.

In order to develop a synthetic sequence that would be compatible with the formation of a 3-pyrrolin-2-one system and also allow modification on the nitrogen, we were interested in utilizing the trimethylsilyllactam **1**[4] and the imino ether **5**. The results of the sulfenylation of **1** and **5** and related lactam chemistry are reported herein.

Reaction of the trimethylsilyllactam **1** with 2 equiv of LDA in THF at −78°C followed by sulfenylation with 1 equiv of phenyl disulfide and subsequent cleavage of the N–Si bond on workup afforded the monosulfide **2** in 29% yield and the

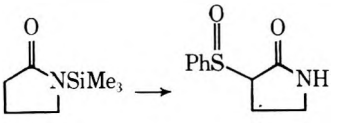


1 **2** **3**

bissulfide **3** in 50% yield. When a 1:2:2 ratio of lactam/base/electrophile was employed, it was found that sulfenylation of **1** gave the bissulfide **3** in 84% yield along with 3% of the monosulfide **2**.

The best yield of the monosulfide was realized when a 1:1:2 ratio of lactam/base/electrophile was used with inverse quenching at 0 °C. In this case, **2** was obtained in a 35% yield and **3** in 33% yield. The results observed by varying the ratio of lactam/base/electrophile with or without the presence of HMPA and with or without inverse quenching are summarized in Table I.

Although the above results with respect to controlling mono- vs. bissulfenylation in the case of silylated lactams were discouraging, the problem could be circumvented, since it was found that sulfinylation of **1** with methyl benzenesulfinate[5]



1 **4**

could be achieved to afford the desired sulfoxide directly. Thus, reaction of **1** with 2 equiv of LDA in THF at −78 °C and subsequent sulfinylation with methyl benzenesulfinate (45 min at −78 °C and room temperature for 2 h) afforded a 67% yield of the crystalline sulfoxide **4**.

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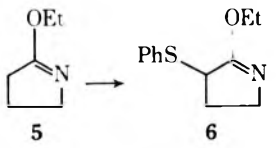
Table I. Sulfenylation of a Trimethylsilyllactam 1

Ratio of lactam/base/electrophile[a]	Equiv of HMPA	Yield, %[b] Mono-2	Bis-3
1:1:1	1	26	44
1:1:1[c,d]	1	20	39
1:1:2[c,e]		35	33
1:2:1		29	50
1:2:1[c,f]		20	55
1:2:2		3	84

[a] PhSSPh. [b] Isolated by column chromatography using silica gel G. [c] Inverse quenching. [d] 35 min at 0 °C and 0.5 h at room temperature. [e] 0 °C for 1.5 h and room temperature for 0.5 h. [f] −40 °C, 1.0 h.

The imino ether **5** can be envisioned as a synthon for the elaboration of the 2-pyrrolidinone nucleus and it also lends itself readily for modification on nitrogen. The bissulfenylation of the imino ether, 2-methoxy-3,4,5,6-tetrahydropyridine, has been reported by Trost and Kunz.[6] We were interested to ascertain if the imino ether **5** could be monosulfenylated under our conditions previously reported[2] for the sulfenylation of lactams, since monosulfenylation is a necessary requirement for the introduction of a $\Delta^{3,4}$ double bond in an intact 2-pyrrolidinone nucleus.

Reaction of the imino ether **5** with 2 equiv of LDA in THF



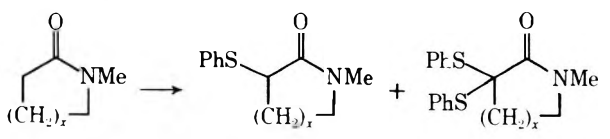
5 **6**

at −78 °C followed by sulfenylation with phenyl disulfide at −78 °C and subsequent warming to −20 °C and then to room temperature afforded a 46% yield of the distilled phenyl sulfide **6**.[7] No bissulfide was detected in this reaction.

Trost and co-workers[8] have shown that in THF solutions bissulfenylation of ketone enolates with phenyl disulfide does not occur regardless of the amount of excess base or disulfide, whereas bissulfenylation in THF–HMPA mixtures can occur. It has also been pointed out by these workers that HMPA effectively increases the rate of sulfenylation. In our earlier work[2] on the sulfenylation of α-methylenelactams in THF–HMPA solutions, it was observed that the ratio of substrate/base/electrophile was critical in controlled mono- vs. bissulfenylation. We therefore were interested in carrying out these sulfenylation reactions in THF alone to determine what role HMPA might have with respect to mono- and bissulfenylation.

These results using different ratios of base and electrophile are summarized in Table II. It appears in this case that HMPA has no effect on promoting bisulfenylation and that the ratio of base to disulfide is very important. Without the utilization of HMPA in these reactions, the purification of the products is much less laborous.

We have also observed that the lactam **7** can be sulfinylated



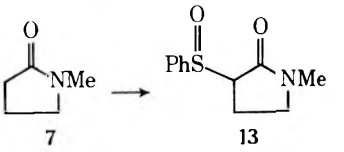
7, x = 1 **9**, x = 1 **11**, x = 1
8, x = 2 **10**, x = 2 **12**, x = 2

in high yield directly with methyl benzenesulfinate,[5] thus circumventing the problems association with bissulfenylation. Reaction of **7** with 2 equiv of LDA in THF at −78 °C and subsequent sulfinylation with methyl benzenesulfinate at −78 °C for 1 h, warming to room temperature, and stirring overnight afforded the crystalline sulfoxide **13** in 94% yield.

Table II. Sulfenylation of *N*-Methyllactams in THF

Substrate	Ratio of lactam/base/electrophile[a]	Compd (yield, %)[b] Mono	Bis
2	1:2:1	**9** (54)	**11** (2)
8	1:2:1	**10** (77)	**12** (0)
7	1:2:2	**9** (6)	**11** (83)
8	1:2:2	**10** (15)	**12** (62)
8	1:2:2[c]	**10** (0)	**12** (76)[d]

[a] PhSSPh. [b] Isolated by column chromatography using silica gel G. [c] Inverse quenching. [d] Isolated by direct crystallization.



7 **13**

Experimental Section

3-Phenylthio-2-pyrrolidinone (2) and 3,3-Diphenylthio-2-pyrrolidinone (3). General Procedure A. A 100-mL three-neck flask fitted with a nitrogen inlet tube, addition funnel, serum cap, and magnetic stirring bar was flamed and deaerated with nitrogen. A solution of diisopropylamine (5.15 g, 0.051 mol) in 30 mL of dry THF was added under N_2, and the reaction vessel was cooled to 0 °C. A hexane solution of 2.4 M *n*-butyllithium (21.23 mL, 0.051 mol) was added with a hypodermic syringe and allowed to stir at 0 °C for 10 min. The reaction mixture was then cooled to −78 °C with a dry ice–acetone bath, and 1-trimethylsilyl-2-pyrrolidinone (4.0 g, 0.0255 mol) dissolved in 10 mL of dry THF was added over a 5-min period. The reaction was allowed to stir at −78 °C for 35 min. Phenyl disulfide (5.55 g, 0.0255 mol) dissolved in 10 mL of THF was added dropwise over a 5-min period, and the addition funnel was then rinsed with 3 mL of THF. The reaction mixture was stirred for an additional 35 min at −78 °C. The reaction was allowed to warm to −20 °C, stirred at −20 °C for 20 min, and then allowed to warm to room temperature. The reaction mixture was poured into 400 mL of H_2O and extracted with three 350-mL portions of ether. The ether extracts were combined and washed consecutively with 150 mL of a 10% NaOH solution, 150 mL of H_2O, 150 mL of a 10% HCl solution, and 150 mL of H_2O. The ether solution was dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator, affording 6.0 g of an oil. The oil was chromatographed on silica gel G and elution with ether–hexane solutions gave 1.9 g (50%) of 3,3-diphenylthio-2-pyrrolidinone (**3**) [mp 100.5–102 °C (Et_2O trituration); NMR ($CDCl_3$) δ 7.92 (s, br, NH, 1 H), 7.10–7.84 (m, 10 H), 3.06 (t, 2 H), and 2.28 (t, 2 H); IR ($CHCl_3$) 3435, 3220, and 1700 (broad) cm^{-1}] and 1.4 g (29%) of 3-phenylthio-2-pyrrolidinone (**2**) [mp 120–120.7 °C (Et_2O–hexane trituration); NMR ($CHCl_3$) δ 7.95 (s, br, NH, 1 H), 7.14–7.75 (m, 5 H), 3.82 (t, 1 H), 3.27 (t, 2 H), and 1.80–2.86 (m, 2 H); IR ($CHCl_3$) 3435, 3224, and 1695 cm^{-1}].

Anal. Calcd for $C_{16}H_{15}NOS_2$: C, 63.76; H, 5.02; N, 4.65. Found: C, 63.72; H, 5.11 N, 4.61.

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.09; H, 5.78; N, 7.24.

3-Phenylthio-2-pyrrolidinone (2) and 3,3-Diphenylthio-2-pyrrolidinone (3). General Procedure B. Inverse Quenching. A 50-mL three-neck flask fitted with an addition funnel, serum cap, and magnetic stirring bar was connected via a glass siphoning tube to a second 100-mL three-neck flask fitted with a nitrogen inlet tube, stopper, and magnetic stirring bar. The apparatus was flamed and deaerated with nitrogen. Phenyl disulfide (5.55 g, 0.0255 mol) dissolved in 20 mL of dry THF was placed in the 100-mL flask. A solution of diisopropylamine (1.29 g, 0.0128 mol) dissolved in 12 mL of THF was placed under nitrogen in the 50 mL-flask and cooled to 0 °C. A hexane solution of 2.4 M *n*-butyllithium (5.31 mL, 0.01274 mol) was added with a hypodermic syringe and allowed to stir at 0 °C for 10 min. The reaction mixture was cooled to −78 °C and 1-trimethylsilyl-2-pyrrolidinone (2.0 g, 0.01274 mol) dissolved in 7 mL of THF was added over a 5-min period. The reaction mixture was stirred for an

additional 0.5 h at −78 °C. The enolate solution was then siphoned through the glass tube into the solution of phenyl disulfide cooled to 0 °C. The resulting reaction mixture was stirred at 0 °C for 1.5 h and then at room temperature for 0.5 h. The reaction mixture was poured into 200 mL of H_2O and extracted with three 175-mL portions of ether. The ether extracts were combined and washed consecutively with 75 mL of a 10% NaOH solution, 75 mL of H_2O, 75 mL of a 10% HCl solution, and 75 mL of H_2O. The ether solution was dried over anhydrous $MgSO_4$ and filtered, and concentration on a rotary evaporator afforded 3.2 g of an oil. The oil was chromatographed on silica gel G, and elution with ether–hexane solutions yielded 630 mg (33%) of 3,3-diphenylthio-2-pyrrolidinone (**3**) and 850 mg (35%) of 3-phenylthio-2-pyrrolidinone (**2**). The NMR and TLC analyses of compounds **2** and **3** were consistent when compared with those of authentic **2** and **3**.

3-Phenylthio-2-pyrrolidinone (2) and 3,3-Diphenylthio-2-pyrrolidinone (3). A 1:1:1 Ratio with HMPA. Following the general procedure A, the amide enolate (0.01274 mol) was prepared in the usual way in 10 mL of dry THF. The reaction mixture was stirred at −78 °C for 10 min. Phenyl disulfide (2.78 g, 0.01274 mol) dissolved in 10 mL of THF containing HMPA (2.28 g, 0.01274 mol) was added over a 10-min period, and the reaction mixture was stirred at −78 °C for 35 min. The reaction mixture was allowed to warm to −20 °C, stirred at −20 °C for 20 min, and then allowed to warm to room temperature.

Workup as usual yielded an oil. The oil was chromatographed on silica gel G, and elution with ether–hexane solutions afforded 840 mg (44%) of **3** and 650 mg (26%) of **2**. The NMR and TLC analyses of compounds **2** and **3** were consistent when compared with those of authentic **2** and **3**.

3-Phenylthio-2-pyrrolidinone (2) and 3,3-Diphenylthio-2-pyrrolidinone (3). Inverse Quenching. A 1:1:1 Ratio with HMPA. Following the general procedure B, the amide enolate (0.01274 mol) was prepared in the usual way in 10 mL of dry THF. The reaction was stirred at −78 °C for 30 min. The enolate solution was then siphoned through a glass tube into a solution of phenyl disulfide (2.78 g, 0.01274 mol) dissolved in 10 mL of THF containing HMPA (2.28 g, 0.01274 mol) at 0 °C. The reaction was stirred at 0 °C for 35 min and then at room temperature for an additional 0.5 h.

Workup as usual yielded an oil. The oil was chromatographed on silica gel G and elution with ether–hexane solutions afforded 750 mg (39%) of **3** and 500 mg (20%) of **2**. The NMR and TLC analyses of compounds **2** and **3** were consistent when compared with those of authentic 2 and **3**.

3-Phenylthio-2-pyrrolidinone (2) and 3,3-Diphenylthio-2-pyrrolidinone (3). Inverse Quenching. A 1:2:1 Ratio. Following the general procedure B, the amide enolate (0.00637 mol) was prepared in the presence of LDA (0.01274 mol) in the usual way in 5 mL of THF. The reaction mixture was stirred at −78 °C for 10 min. The enolate solution was then siphoned through a glass tube into a solution of phenyl disulfide (1.39 g 0.00637 mol) dissolved in 10 mL of THF at −40 °C. The resulting reaction mixture was stirred at −40 °C for 1 h.

Workup as usual yielded an oil. The oil was chromatographed on silica gel G and elution with ether–hexane solutions afforded 525 mg (55%) of **3** and 245 mg (20%) of **2**. The NMR and TLC analysis of compounds **2** and **3** were consistent when compared with those of authentic 2 and **3**.

3-Phenylthio-2-pyrrolidinone (2) and 3,3-Diphenylthio-2-pyrrolidinone (3). A 1:2:2 Ratio. Following the general procedure A, the amide enolate (0.00637 mol) was prepared in the presence of LDA (0.0127 mol) in the usual way in 5 mL of THF. The reaction mixture was stirred at −78 °C for 35 min. Phenyl disulfide (2.77 g, 0.0127 mol) dissolved in 10 mL of THF was added dropwise over a 10-min period, and the reaction mixture was stirred at −78 °C for 35 min. The reaction mixture was allowed to warm to −20 °C, stirred at −20 °C (CCl_4–dry ice bath) for 20 min, and then allowed to warm to room temperature over a 40-min period. Workup as usual yielded an oil. The oil was chromatographed on silica gel G and elution with ether–hexane solutions afforded 1.6 g (84%) of **3** and 0.03 g (3%) of **2**. The NMR and TLC analyses of compound **3** were consistent when compared with those of authentic **3**.

3-Phenylsulfinyl-2-pyrrolidinone (4). Following the general procedure A, LDA (0.0446 mol) was prepared in the usual way in 10 mL of THF. The reaction mixture was cooled to −78 °C and 1-trimethylsilyl-2-pyrrolidinone (3.5 g, 0.0223 mol) dissolved in 15 mL of THF was added over a 10-min period. The reaction mixture was allowed to stir at −78 °C for 45 min, then allowed to come to room temperature, and stirred for 2 h.

The reaction was poured into 100 mL of a 10% sodium bicarbonate solution and extracted with three 350-mL portions of $CHCl_3$. The chloroform extracts were combined, washed with a dilute solution of HCl and a saturated NaCl solution, dried over anhydrous $MgSO_4$, and filtered, and concentration on a rotary evaporator afforded a brown oil. The oil was chromatographed on silica gel G, and elution with ether–methanol solutions afforded 3.1 g (67%) of **4** as a white solid: NMR ($CDCl_3$) δ 7.05–7.85 (m, 6 H), 3.20–3.75 (m, 3 H), and 1.52–3.17 (m, 2 H); IR ($CHCl_3$) 3340, 3325, 1710, and 1045 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N, 6.69. Found: C, 57.42; H, 5.38; N, 6.72.

2-Ethoxy-3-phenylthio-1,2-dehydropyrrolidine (6). A 1:2:1 Ratio with HMPA. Following the general procedure A, the imidate anion (0.0354 mol) was prepared in the presence of LDA (0.0708 mol) in the usual way in 30 mL of dry THF. The reaction mixture was stirred at −78 °C for 35 min. Phenyl disulfide (7.72 g, 0.0354 mol) dissolved in 15 mL of THF containing HMPA (6.34 g, 0.0354 mol) was added over a 7-min period. The addition funnel was rinsed with 5 mL of THF, and the resulting reaction mixture was stirred at −78 °C for 35 min. The reaction mixture was allowed to warm to −20 °C, stirred at −20 °C for 20 min, and then allowed to warm to room temperature. Workup as usual yielded an oil. The oil was distilled twice to afford 3.6 g (46%) of **6**: bp 95–100 °C (0.05 mm); NMR (CCl_4) δ 7.05–7.58 (m, 5 H), 4.13 (q), and 3.73–3.96 (m, 3 H), 3.39 (t, 2 H), 1.62–2.76 (m, 2 H) and 1.27 (t, 3 H).

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.32. Found: C, 65.08; H, 6.74; N, 6.20.

1-Methyl-3-phenylthio-2-pyrrolidinone (9) and 1-Methyl-3,3-diphenylthio-2-pyrrolidinone (11). A 1:2:1 Ratio. Following the general procedure A, the enolate of *N*-methyl-2-pyrrolidinone (0.0404 mol) was prepared in the presence of LDA (0.0808 mol) in the usual manner in 30 mL of THF. The reaction mixture was stirred at −78 °C for 35 min. Phenyl disulfide (8.81 g, 0.0404 mol) dissolved in 20 mL of THF was added dropwise over a 10-min period. The reaction mixture was stirred at −78 °C for 35 min. The reaction mixture was allowed to warm to −20 °C, stirred at −20 °C for 20 min, and then allowed to warm to room temperature.

Workup as usual yielded an oil. The oil was chromatographed on silica gel G, and elution with ether–hexane solutions and ether afforded 4.5 g (54%) of **9** and 141 mg (2%) of **11**. The NMR and TLC analyses of compounds **9** and **11** were consistent when compared with those of authentic[2] **9** and **11**.

1-Methyl-3-phenylthio-2-piperidone (10). A 1:2:1 Ratio. Following the general procedure A, the enolate of 1-methyl-2-piperidone (0.0354 mol) was prepared in the presence of LDA (0.0707 mol) in the usual way in 35 mL of THF. The reaction mixture was stirred at −78 °C for 35 min. Phenyl disulfide (7.72 g, 0.0354 mol) dissolved in 20 mL of THF was added over a 15-min period. The reaction mixture was stirred at −78 °C for 35 min. The reaction mixture was allowed to warm to −20 °C, stirred at −20 °C for 20 min, and then allowed to warm to room temperature.

Workup as usual yielded an oil. The oil was chromatographed on silica gel G and elution with ether–hexane and ether solutions afforded 6.0 g (77%) of **10**, bp 155 °C (0.05 mm). The NMR and TLC analyses of compound **10** were consistent when compared with those of authentic[2] **10**.

1-Methyl-3-phenylthio-2-pyrrolidinone (9) and 1-Methyl-3,3-diphenylthio-2-pyrrolidinone (11). A 1:2:2 Ratio. Following the general procedure A, the enolate of 1-methyl-2-pyrrolidinone (0.040 mol) was prepared in the presence of LDA (0.080 mol) in the usual manner in 35 mL of THF. The reaction mixture was stirred at −78 °C for 35 min. Phenyl disulfide (17.6 g, 0.080 mol) dissolved in 35 mL of THF was added dropwise over a 15-min period. The reaction mixture was stirred at −78 °C for 35 min. The reaction mixture was allowed to warm to −20 °C, stirred at −20 °C for 20 min, and then allowed to warm to room temperature.

Workup as usual yielded a white solid. The solid was triturated with a 50% ether–hexane solution to afford 9.2 g (72%) of **11**, mp 87–88.5 °C. The mother liquor was chromatographed on silica gel G, and elution with ether and methanol–ether solutions afforded an additional 1.4 g (11%) of **11** and 460 mg (6%) of **9**. Total yield of **11** was 83%. The NMR and TLC analyses of compounds **9** and **11** were consistent when compared with those of authentic[2] **9** and **11**.

1-Methyl-3,3-diphenylthio-2-piperidone (12). A 1:2:2 Ratio. Following the general procedure A, the enolate of 1-methyl-2-piperidone (0.0354 mol) was prepared in the presence of LDA (0.0707 mol) in the usual way in 50 mL of dry THF. The reaction mixture was stirred at −78 °C for 35 min. Phenyl disulfide (15.41 g, 0.0707 mol) dissolved in 35 mL of THF was added over a 15-min period. The reaction mixture was stirred at −78 °C for 35 min. The reaction mixture was allowed to warm to −20 °C, stirred at −20 °C for 20 min, and then

allowed to warm to room temperature. Workup as usual yielded a white solid. Trituration of the solid with a 50% ether–hexane solution afforded 6.5 g (56%) of **12**, mp 136–137 °C. The mother liquor was chromatographed on silica gel G, and elution with ether–hexane solutions and ether afforded an additional 675 mg (3%) of **12** and 1.2 g (15%) of **10**. Total yield of **12** was 62%. The NMR and TLC analyses of compounds **10** and **12** were consistent when compared with those of authentic[2] **10** and **12**.

1-Methyl-3,3-diphenylthio-2-piperidone (12). Inverse Quenching. A 1:2:2 Ratio. Following the general procedure B, the amide enolate (0.00885 mol) was prepared in the usual way in 13 mL of THF in the presence of LDA (0.0177 mol). The reaction was stirred at −78 °C for 10 min. The enolate solution was siphoned through a glass tube into a solution of phenyl disulfide (3.85 g, 0.0177 mol) dissolved in 10 mL of THF at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1.5 h. Workup as usual yielded a solid. The solid was triturated with a 50% ether–hexane solution to afford 2.2 g (76%) of **12**, mp 136–37.5 °C. The NMR and TLC analyses of compound **12** were consistent when compared with those of authentic[2] **12**.

1-Methyl-3-phenylsulfinyl-2-pyrrolidinone (13). Following the general procedure A, LDA (0.0202 mol) was prepared in the usual manner in 10 mL of THF. The reaction mixture was cooled to −78 °C and 1-methyl-2-pyrrolidinone (1 g, 0.0101 mol) dissolved in 20 mL of THF was added over a 15-min period. The reaction mixture was allowed to stir at −78 °C for 1 h. Methyl benzenesulfinate (1.57 g, 0.0101 mol) dissolved in 5 mL of THF was added over a 5-min period. The reaction was stirred at −78 °C for 1 h, then allowed to come to room temperature, and stirred overnight. The reaction mixture was poured into a 10% hydrochloric acid solution and extracted with two 200-mL portions of $CHCl_3$. The chloroform extracts were combined, washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator, affording a yellow oil. The oil was chromatographed on silica gel G, and elution with ether–hexane solutions, ether, and ether–chloroform solutions afforded 2.2 g (96%) of pure **13** as a white solid: the NMR and TLC analyses of **13** were consistent when compared with those of authentic **13**.[3]

Registry No.—**1**, 14468-90-7; **2**, 65102-72-9; **3**, 65102-73-0; **4**, 65102-74-1; **5**, 931-46-4; **6**, 65138-32-1; **7**, 872-50-4; **8**, 931-20-4; **9**, 59953-50-3; **10**, 59953-51-4; **11**, 59953-53-6; **12**, 59953-54-7; **13**, 63914-40-9; **14**, 65102-75-2; phenyl disulfide, 882-33-7; methyl benzenesulfinate, 670-98-4.

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(1) Undergraduate research participant.
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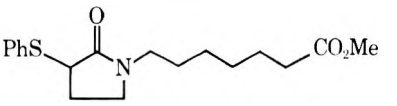
(7) Reaction of the phenyl sulfide **6** with methyl 7-bromoheptanoate in refluxing xylene afforded the lactam **14**: NMR (CCl_4) δ 6.90–7.60 (m) and 3.59 (s, OCH_3). For an analogous *N*-alkylation, see: L. A. Paquette, T. Kakihana, and J. F. Kelly, *J. Org. Chem.*, **36**, 437 (1971).



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Clarification of the Mechanism of the Reaction of Terminal Propargylic Chlorides with Alkyl Grignard Reagents

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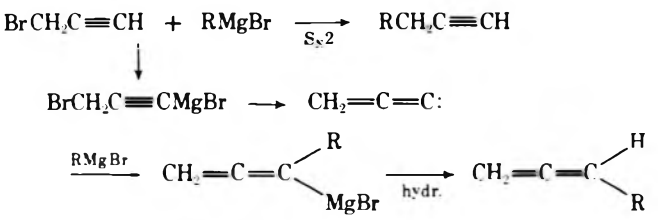
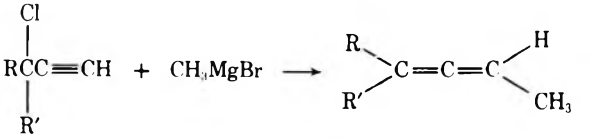
In the absence of transition metal impurities in the magnesium used to prepare the alkyl Grignard reagent, terminal propargylic chlorides react with Grignard reagents to form an allene carbene–zwitterion intermediate. Reaction of this intermediate with a second molecule of the Grignard reagent generates a mixture of propargyl and allenyl Grignard reagents which on hydrolysis generates a mixture of two alkynes and the allene. No evidence was found for the occurrence of carbonium ion, free radical, or S_N2' reaction pathways.

The history of the reaction of propargyl derivatives with Grignard reagents is one of confusion, widely divergent results being reported by various authors. Serratosa[1] has suggested that propargyl bromide can react with Grignard reagents via two mechanistic pathways, one being a direct S_N2 process to



produce exclusively alkyne, and the other occurring via an allene–carbene to give exclusively allene. Pasternak and Delépine[2] have reported that terminal tertiary propargylic halides react with methylmagnesium bromide to produce only allene in quantitative yields! (No mechanism was proposed.) These authors also suggested that the previous contradictory reports of the formation of mixtures of isomeric allenes, al-



kynes, and dienes were due to isomerization during the hydrolysis step.

Coulomb-Delbecq[3] and co-workers have investigated the reactions of propargylic acetates with Grignard reagents in the absence and presence of added magnesium iodide or cobalt chloride. In the presence of added magnesium iodide a mixture of products is obtained in which allene and alkyne are formed in greater amounts than in the absence of magnesium iodide, leading the authors to propose that a propargyl–allenyl cation was an intermediate. However, in the presence of cobalt chloride substantially higher yields of allene were formed, leading the authors to suggest that an intermediate propargyl–allenyl radical was involved as an intermediate. Substantial yields of dimeric products were also reported in both cases.

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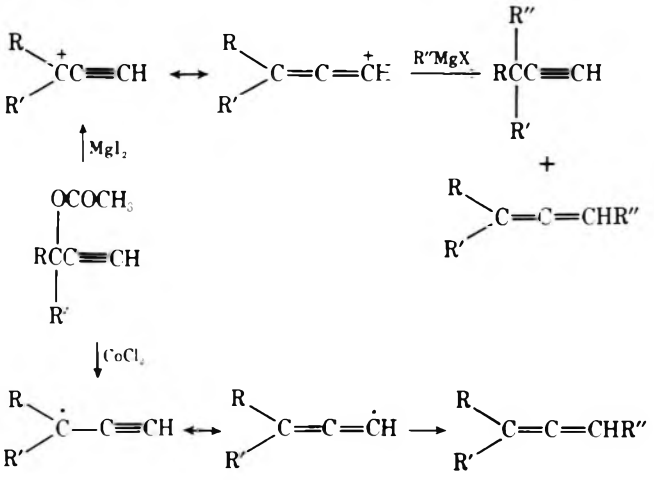


The reactions of nonterminal propargylic halides with Grignard reagents have been studied by Zakharova[4] and by Jacobs and Meyers.[5] Zakharova[4] reported that allenes are the major products formed and suggested a carbocation intermediate mechanism. Jacobs and Meyers[5] reported that alkynes and dienes were the major products; the dienes later were shown to be derived by isomerization of the initially formed allenes.[6]

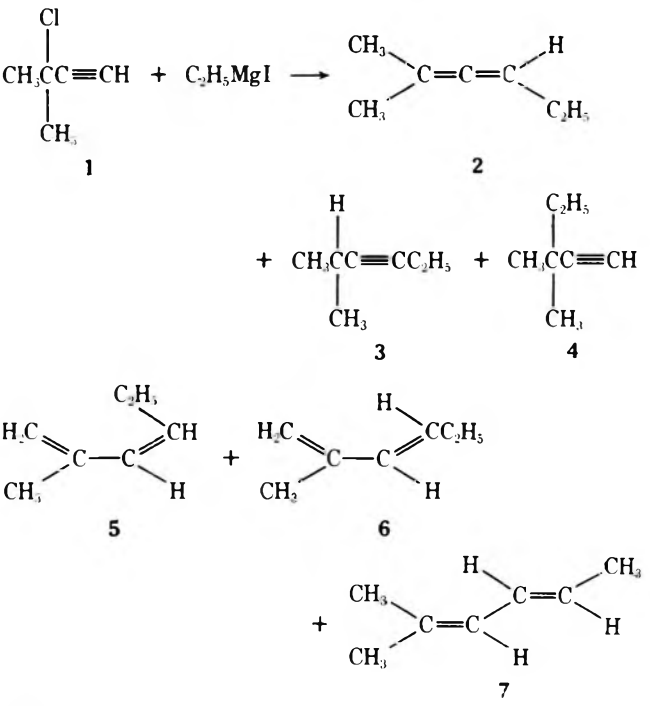
Finally, apparently accepting that allenes are formed in the reactions of propargylic halides with Grignard reagents, an S_N2'-type mechanism has also been suggested to account for their formation.[7]

In view of our need to develop a reliable synthesis of allenes, and the diverse results reported in the literature, we undertook a detailed study of the reaction of selected propargylic halides with Grignard reagents. During the course of this study we have derived evidence in favor of the allene–carbene mechanism for the direct reaction of Grignard reagents with terminal propargylic halides leading to the formation of a mixture of alkynes and allene, and a transition metal catalyzed process resulting in the exclusive formation of allene.[8] We describe herein the results of the study of the noncatalyzed reaction, while the study of the transition metal catalyzed reactions is described in detail in the accompanying article.[9]

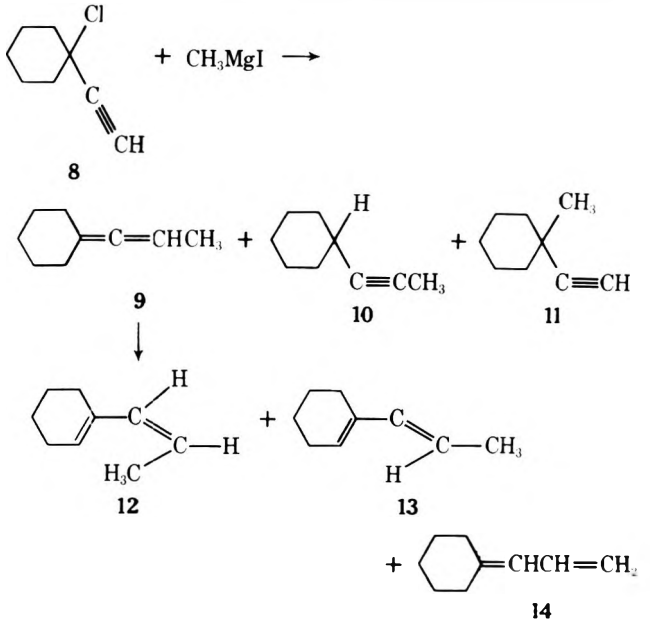
Results

Initial results derived from reactions of propargyl halides with Grignard reagents in our laboratories were not consistent. In some instances mixtures of alkynes and allene, and in some cases dienes, were formed, while in others only allene was formed. It finally became apparent that internally consistent, but different, results were being obtained using two different sources of magnesium, and that allene formation was the abnormal reaction in which transition metal catalysis was occurring.[8,9] Only the results of the noncatalyzed reactions are described here.

Treatment of 3-chloro-3-methyl-1-butyne (**1**) with 2 molar equiv of ethylmagnesium iodide at 0 °C resulted in the slow evolution of ethane. At the end of 24 h gas evolution had ceased. Hydrolysis of an aliquot of the reaction mixture indicated that ~75% of the Grignard reagent had been consumed. Distillation of the reaction product produced a volatile fraction containing **2, 3,** and **4** which were separated by preparative GLPC and identified by their spectral properties. The distillation residue was analyzed and separated by GLPC and shown to contain, in addition to **2**, the three dienes **5, 6,** and **7**. GLPC analysis of the crude reaction mixture immediately after hydrolysis showed the presence of only **2, 3,** and **4** in a 59:15:26 ratio. In contrast to the earlier suggestion that isomerization of the allene to dienes occurred during the hydrolysis step,[2] the ratio of **2:3:4** remained the same regardless of whether the reaction mixture was quenched with water, 5% sulfuric acid, saturated ammonium chloride, or 5% sodium hydroxide in either a normal or inverse manner. The isomerization of the allene appears to be a thermal process and is under further study in our laboratories. Quenching a reaction mixture with deuterium oxide followed by determination of the deuterium content in **2, 3,** and **4** by mass spectrometry showed the presence of 47.0% **2**-d_1, 48.8% **3**-d_1 and 8.9% **4**-d_1.



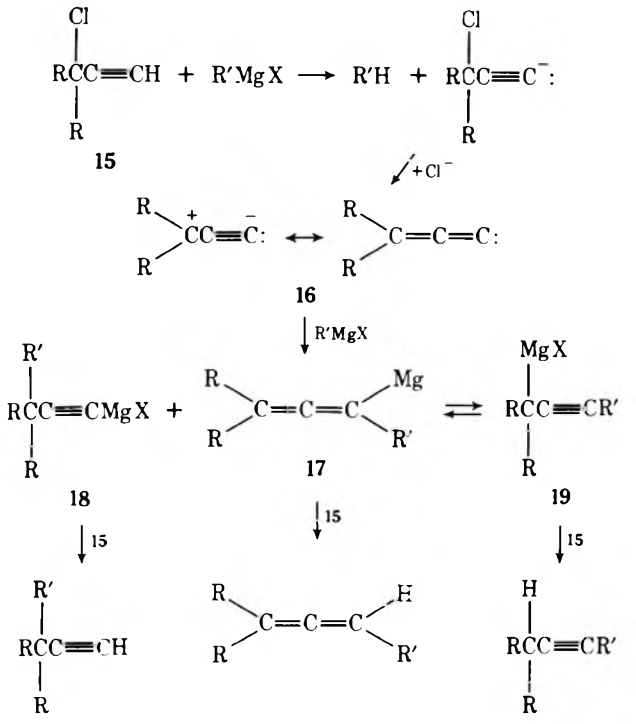
In a similar manner, 1-ethynylcyclohexyl chloride (**8**) on



reaction with 2 molar equiv of methylmagnesium iodide for 19.5 h at 0 °C produced **9, 10,** and **11** in a 100:15:46 ratio, along with lesser amounts of the rearranged dienes **12, 13,** and **14.**

Discussion

The formation of the isomeric alkynes and allene as the primary products from the tertiary propargylic halides is best rationalized as occurring via a zwitterion–allene carbene intermediate (**15**) which is formed by proton abstraction of the acetylenic hydrogen by the Grignard reagent followed by loss of chloride ion.[10] Nucleophilic attack on **16** by a second molecule of the Grignard reagent at either the propargyl or allenyl



carbon[11] produced the new organomagnesium intermediates **17**, **18**, and **19**. The incomplete utilization of 2 molar equiv of the Grignard reqgent, and the incomplete deuterium incorporation on deuterolysis, is due to the fact that the newly formed Grignard reagents **17–19** compete with the original Grignard reagent in proton abstraction from the propargyl halide.

The competitive proton abstraction by **17** unfortunately does not allow one to gain any information concerning the possible formation of allene via an S_N2' displacement process. Accordingly, we reinvestigated the reaction of propargyl bromide with a Grignard reagent as reported by Serratosa.[1] As reported, only allene is formed (<1% of any isomeric alkyne was present). However, careful analysis of the reaction mixture showed that *no* hexane had been formed as would have been required by the allene carbene mechanism. The formation of only allene is most consistent with its being formed via a transition metal catalyzed process,[9] propargyl bromide being very much more reactive than the propargyl chlorides in the transition metal catalyzed process and thus occurring at much lower concentrations of transition metal impurities in the magnesium. At best, an S_N2' process cannot be occurring to more than a few percent, even in the most favorable cases.

Experimental Section

Reaction of 3-Chloro-3-methyl-1-butyne (1) with Ethylmagnesium Iodide. To a solution of 0.25 mol of ethylmagnesium iodide in 135 mL of ether was rapidly added 10.25 g (0.1 mol) of **1** at 0 °C. The reaction mixture was allowed to warm to room temperature during which slow gas evolution ensued (mostly ethane containing a small amount of butane by mass spectroscopy). After 24 h gas evolution had ceased. An aliquot of the reaction mixture was removed and hydrolyzed in a gas evolution apparatus indicating ~75% consumption of the ethylmagnesium iodide. The reaction mixture was hydrolyzed by the cautious addition of cold water (30 mL). The organic layer was decanted, washed once with water and saturated NaCl, and dried ($MgSO_4$). The ether was removed by distillation and the residue was distilled (63–95 °C) giving 2.48 g of a colorless liquid and 3.95 g of distillation residue. Analysis of the distillate by GLPC on a 10-ft Carbowax 20M column showed the presence of **4** (26.6%), **3** (15.5%), and **2** (58.9−) which were isolated by preparative GLPC.

4: NMR ($CDCl_3$) δ 0.98 (distorted triplet, J = 6.5 Hz, 3 H), 1.17 (s, 6 H), and 1.47 (distorted quartet, J = 6.5 Hz, 2 H), and 2.07 (s, 1 H); MS M^+· 96.

3: NMR ($CDCl_3$) δ 1.11 (t, J = 6.7 Hz, 3 H), 1.14 (d, J = 6.3 Hz, 6 H) and 2.18 (s, J = 6.3 Hz, 1 H); MS M^+· 96.

2: NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3 H), 1.67 (d, J = 2.7 Hz, 6 H), 1.97 (m, 2 H), and 5.02 (m, 1 H); MS M^+· 96.

GLPC analysis of the distillation residue showed the presence of allene **2**, dienes **5** and **6**, and **7** in a ratio of 0.26:0.45:1.00. **5**, **6**, and **7** were isolated by preparative GLPC.

5: NMR ($CDCl_3$) δ 0.98 (t, J = 6.7, 3 H), 1.89 (m, 3 H), ~2.13 (m, 2 H), 4.86 (m, 1 H), 4.97 (m, 1 H), 5.46 (m, 1 H), and 5.84 (broadened doublet, J = 12.2 Hz, 1 H); MS M^+· 96.

6: NMR ($CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 3 H), 1.82 (m, 3 H), 2.14 (dq, J = 7.2, 5.9 Hz, 2 H), 4.87 (m, 2 H), 5.74 (dt, J = 16.8, 5.9 Hz, 1 H), and 6.16 (d, J = 16.8 Hz, 1 H); MS M^+· 96.

7: NMR ($CDCl_3$) δ 1.72 (overlapping broad singlets, 6 H), 1.78 (broad singlet, 3 H), 5.49 (bdd, J = 14.8, 6.6 Hz, 1 H), 5.9 (dm's, J = 14.8, ~1.5 Hz, 1 H), and 6.23 (ddq, J = 14.8, 10.6, 1.5 Hz, 1 H); MS M^+· 96.

GLPC analysis of the crude reaction product immediately after hydrolysis indicated the presence of essentially only **3**, **2**, and **4** in a 26:59:15 ratio. The product distribution remains the same regardless of whether the reaction mixture is quenched with water, 5% sulfuric acid, saturated ammonium chloride, or 5% sodium hydroxide.

Deuterolysis of Reaction of 1 with Ethylmagnesium Iodide. The reaction of **1** with ethylmagnesium iodide was carried out as described above except that hydrolysis was carried out by addition of 20 mL of deuterium oxide. **2**, **3**, and **4** were isolated by preparative GLPC and their deuterium content was determined by mass spectrometry indicating the presence of 8.9% **4**-d_1, 48.8% **3**-d_1, and 47.0% **2**-d_1.

Reaction of 1-Ethynylcyclohexyl Chloride (8) with Methylmagnesium Iodide. To 0.1 mol of methylmagnesium iodide in 150 mL of ether was added 0.04 mol of 1-ethynylcyclohexyl chloride (**8**). A slow evolution of methane (identified by MS analysis) ensued. Aliquots were periodically removed, hydrolyzed, and analyzed by GLPC on a 10-ft Carbowax 20M column for unreacted **8**. After stirring for 19.5 h at 25 °C the reaction was complete. The reaction mixture was hydrolyzed by the addition of 25 mL of water. The organic layer was removed, washed twice with water, and dried ($MgSO_4$), and the solvent removed under reduced pressure giving a pale yellow liquid (85%). Analysis by GLPC showed the presence of **9–14** in a 100:15:46:1:12:9 ratio. The products were separated by preparative GLPC and characterized by IR, NMR, and MS.

9: NMR ($CDCl_3$) δ 1.56 (bm, 6 H), 1.59 (d, J = 7.0 Hz, 3 H). 2.11 (m, 4 H), 4.91 (quartet of quintets, J = 7.0, 2.2 Hz, 1 H); IR (cap film) 1920 cm^{-1} ($\nu_{C=C=C}$); MS calcd for C_9H_{14} 122.1096, obsd 122.1098.

10: NMR ($CDCl_3$) δ 1.56 (s, 3 H), 1.5–1.8 (bm, 11 H); MS calcd for 122.1096, obsd 122.1098.

11: NMR ($CDCl_3$) δ 1.19 (s, 3 H), 1.58 (bm, 10 H), and 2.07 (s, 1 H); IR (cap film) 3330 ($\nu_{\equiv C-H}$) and 2110 cm^{-1} ($\nu_{C\equiv C}$); MS calcd for 122.1096, obsd 122.1097.

12: NMR ($CDCl_3$) δ 1.62 (m, 4 H), 1.79 (d, J = 7.2 Hz, 3 H), 2.14 (m, 4 H), 5.32 (dq, J = 12.3, 7.2 Hz, 1 H), 5.65 (m, 1 H), and 5.78 (bd, J = 12.3 Hz, 1 H); MS M^+· 122.

13: NMR ($CDCl_3$) δ 1.62 (m, 4 H), 1.75 (d, J = 6.2 Hz, 3 H). 2.11 (m, 4 H), 5.56 (dq, J = 15.4, 6.2 Hz, 1 H), 5.61 (m, 1 H), and 6.05 (bd, J = 15.4 Hz, 1 H); MS M^+· 122.

14: NMR ($CDCl_3$) δ 1.62 (m, 6 H), 2.10 (m, 4 H), 4.8–5.2 (m, 3 H); MS M^+· 122.

Registry No.—**1**, 1111-97-3; **2**, 29212-09-7; **3**, 36566-80-0; **4**, 918-82-1; **5**, 65150-07-4; **6**, 20626-38-4; **7**, 32763-68-1; **8**, 6209-75-2; **9**, 20023-43-2; **10**, 18736-95-3; **11**, 28509-10-6; **12**, 5680-41-1; **13**, 54354-35-7; **14**, 5664-10-8.

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Transition Metal Catalysis in Allene Formation from Grignard Reagents and Propargyl Chlorides[1]

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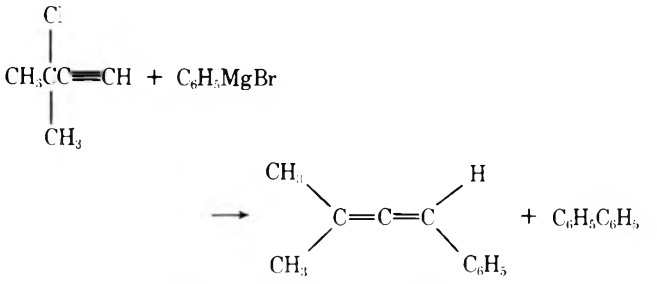
In the presence of catalytic quantities of iron, cobalt, nickel, and copper salts Grignard reagents react with propargyl chlorides to produce allenes. Alkynes are generally not formed. Chromium, manganese, rhodium, and silver salts do not catalyze the reaction. A mechanism for allene formation is proposed involving initial formation of a low valence state metal species from reaction of the Grignard reagent with the metal salt, which undergoes oxidative insertion into the carbon–chlorine bond of the propargyl chloride. Displacement of halogen by alkyl from the Grignard reagent forms a bisorganometal species which is proposed to decompose to allene. Evidence in support of this mechanism is discussed.

Introduction

In the preceding article,[2] a brief review was given of the diverse results reported on the reactions of propargylic halides with Grignard reagents, and the results of studies in our laboratories on the reactions of terminal, tertiary propargylic halides with Grignard reagents were presented and discussed. In that study it was shown that the terminal propargylic halides react slowly with Girgnard reagents to form a zwitterion–allene carbene intermediate which undergoes nucleophilic attack by a second molecule of the Grignard reagent at either the propargylic or allenyl carbon atoms to produce new organomagnesium species. The newly formed Grignard species either abstract a proton from the propargylic halide or under hydrolysis to produce mixtures of two isomeric alkynes and allene.

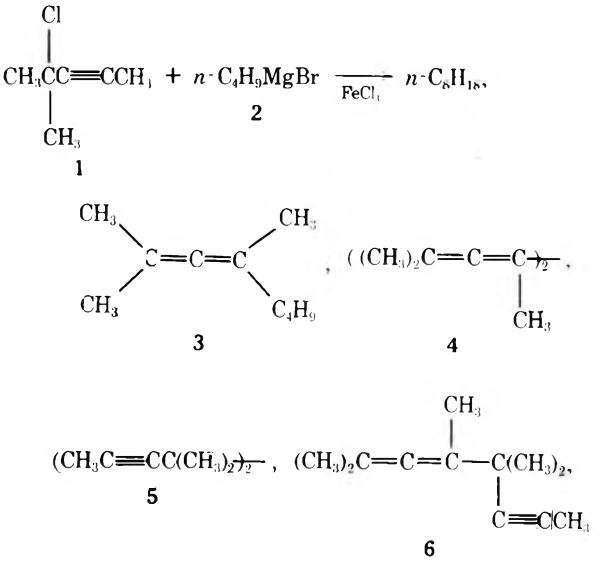
During our initial studies it was observed that 3-chloro-3-methyl-1-butyne reacted with phenylmagnesium bromide to form 1,1-dimethyl-3-phenylallene and biphenyl in excellent yield. The formation of the biphenyl initially suggested that



a single electron transfer (SET), free-radical process was occurring. Utilizing the observation of Ashby and co-workers that ferric ion catalyzes SET reactions between Grignard reagents and benzophenones,[3] ferric chloride was added to the reactions of propargylic halides with alkyl Grignard reagents in an attempt to catalyze the supposed electron transfer, free-radical process in those cases. The rates of the reactions in the presence of ferric chloride were tremendously accelerated, and excellent yields of allenes uncontaminated by alkynes were obtained.[4] Although it was initially thought that these reactions were SET, free-radical processes, further considerations (vide infra) militated against this, and an organometallic intermediate, catalytic cycle mechanism evolved. Our initial studies with ferric chloride catalysis have been extended to include other transition metal salts, the results of which are reported herein along with a discussion of the catalysis mechanism. With the discovery of the transition metal catalysis the seemingly contradictory results previously reported for the reactions of propargylic halides with Grignard reagents are readily understood.

Results

Initial studies were carried out on the reaction of 4-chloro-4-methyl-2-pentyne (1) with *n*-butylmagnesium bromide in ether solution at 0 °C to determine optimum conditions for formation of allene. Addition of 0.07 mol of 1 to 0.085 mol of Grignard reagent containing as little as 2.5×10^{-6} mol of ferric chloride or ferric acetonylacetate [$Fe(Acac)_3$] resulted in a nearly instantaneous reaction. Immediate analysis by GLPC after completion of the addition of 1 showed the reaction to be complete. GLPC analysis of the product showed the presence of octane (up to 5%), allene **3**, and four C_{12} dimers



and rearranged dimer

of 1 (up to 5% total yield). Three of the dimers are assigned structures **4–6** on the basis of their NMR spectra. The fourth dimer is believed to be an allene rearrangement product of either **4** or **6**. GLPC analysis of a hydrolyzed aliquot of the Grignard solution before addition of 1 showed the presence of only trace amounts of *n*-butyl bromide or octane. Inverse addition of **2** to 1 yielded the same results.

In addition to the facile iron(III) catalyzed reactions of 1 with primary alkylmagnesium halides, secondary alkyl Grignard reagents also react in a similar, but slower manner. Higher yields of the propargyl dimers **4–6** are formed during the reactions with the secondary alkyl Grignard reagents. Alkylation with *tert*-butylmagnesium bromide could not be affected.

All structural variations of propargyl chlorides have been studied. Terminal primary, secondary, and tertiary propar-

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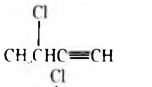
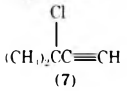
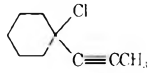
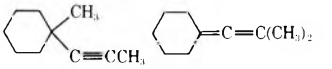
Table I. Reactions of Propargylic Chlorides with Grignard Reagents in the Presence of Fe(III)[a]

Entry	Propargyl chloride	Registry no.	Grignard reagent	Catalyst	Addition time, min	Product	Yield, %
1	$ClCH_2C{\equiv}CH$	624-65-7	n-C_4H_9MgBr	$FeCl_3$	10	$H_2C{=}C{=}CH(n\text{-}C_4H_9)$	85
2	$ClCH_2C{\equiv}CH$		sec-C_4H_9MgBr	$FeCl_3$	60	$H_2C{=}C{=}CH(sec\text{-}C_4H_9)$	70
3		21020-24-6	n-C_4H_9MgBr	$FeCl_3$	10	$CH_3CH{=}C{=}CH(n\text{-}C_4H_9)$	80
4	 (7)	1111-97-3	C_2H_5MgI	$FeCl_3$	10	$(CH_3)_2C{=}C{=}CHC_2H_5$	80
5	7		n-C_4H_9MgBr	$FeCl_3$	10	3	80–90
6	7		n-C_4H_9MgBr	$Fe(Acac)_3$	30	3	60
7	7		sec-C_4H_9MgBr	$FeCl_3$	60	$(CH_3)_2C{=}C{=}CH(sec\text{-}C_4H_9)$	75
8	1	999-79-1	CH_3MgI	$FeCl_3$	10	$(CH_3)_3CC{\equiv}CCH_3$, $(CH_3)_2C{=}C{=}C(CH_3)_2$	90[b]
9	1		n-C_4H_9MgBr	$FeCl_3$	20	$(CH_3)_2C{=}C{=}C(CH_3)(n\text{-}C_4H_9)$	87
10	1		i-C_3H_7MgBr	$FeCl_3$	60	$(CH_3)_2C{=}C{=}C(CH_3)(i\text{-}C_3H_7)$	88
11	1		t-C_4H_9MgBr	$FeCl_3$	240	...	...[c]
12		60820-36-2	CH_3MgI	$FeCl_3$	10		90[b]

[a] Reaction temperature 25 °C. Catalyst added as THF solution. [b] Alkyne and allene formed in a 1:1 ratio. [c] No reaction after the indicated time.

Table II. Relative Reactivities of Propargyl Chlorides with n-Butylmagnesium Bromide in the Presence of Fe(III)

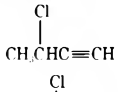
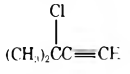
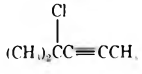
Propargyl chloride	Relative reactivity
$ClCH_2C{\equiv}CH$	30
	19.7
	8
	1

Table III. Reactivity of Transition Metal Catalysts on the Reaction of 1 and 7 with 2

Catalyst	Propargyl chloride	Addition time, min	Allene yield, %	Dimer yield, %
$FeBr_2$	1	20	80	8
$CoBr_2$	1	60	55	...[a]
$Co(Acac)_2$	7	60	30–40	...[a]
$NiBr_2$	7	60	90	...[a]
$Ni(Acac)_2$	7	60	95	<2
CuCl	7	30	55	...[a]
CuCl	1	30	50	30
$CuBr_2$	7	30	90	...[a]
$CuBr_2$	1	30	50	23
$MnCl_2$	7		...[b]	
$CrCl_3$	7		...[b]	
$RhCl_2$	7		...[b]	
$Rh[P(C_6H_5)_3]Cl$	7		...[b]	
AgO_2CCH_3	7		...[b]	

[a] Not measured. [b] No observed catalytic reaction.

gylic chlorides react with methyl, primary, and secondary alkyl Grignard reagents in the presence of iron(III) to produce good to excellent yields of allene. Nonterminal tertiary propargylic halides react with methylmagnesium iodide in the presence of iron(III) to produce 1:1 mixtures of alkyne and allene (entries 8 and 12 in Table I). In contrast, these same chlorides react with n-butyl, isopropyl, or sec-butyl Grignard reagents in the presence of iron(III) to produce only allene.

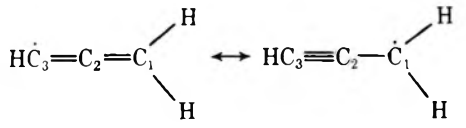
Relative reactivities of variously substituted propargyl chlorides with n-butylmagnesium bromide in the presence of iron(III) have been determined using competitive reaction techniques under identical reaction conditions and extrapolated to zero reaction time. The results are given in Table II.

A number of other transition metal halides and acetonylacetonates have been tested for catalytic activity in the reaction of 1 and 7, the results of which are given in Table III. It is particularly interesting to note that both Fe(III) and Fe(II), and Cu(II) and Cu(I), salts catalyze the reaction, in each case with the same apparent degree of efficiency. Of the transition metals which did catalyze the reaction, the catalytic efficiency decreases markedly in the sequence Fe > Co > Ni > Cu. In the reactions catalyzed by iron, the reaction proceeded very rapidly, regardless of whether the Grignard reagent was added to the chloride or vice versa. With cobalt, the reaction proceeded less rapidly, but still proceeded in the presence of excess Grignard reagent. In the case of nickel and copper, catalytic activity is maintained *only* when the Grignard reagent is added very slowly to the chloride–catalyst solution in order to avoid the presence of an excess of the Grignard reagent. When the Grignard reagent is added too rapidly, catalytic activity is lost. Addition of more catalyst at this point fails to generate catalytic activity. Addition of nickel and copper catalysts to a premixed solution of chloride and Grignard reagent is ineffective.

Attempts were made to detect catalytic coupling of n-butylmagnesium bromide (2) with halides. None was observed. The direct reaction of 2 with allyl bromide is sufficiently rapid that possible Fe(III) catalysis could not be observed. No catalysis was evident in the reaction of 2 with benzyl bromide.

Discussion

Although it was first thought that allene formation was occurring via a SET, radical intermediate process, the properties of the intermediate propargyl–allenyl radical (8) were not consistent with the formation of only allene in a radical abstraction or combination process. Ab initio calculations on



8

8 indicate slightly greater spin density exists on C_1.[5] INDO calculations carried out in our laboratories on 8 and 1,1-dimethyl radical indicate that ~61% and ~56% of the spin density resides on C_1, respectively. ESR data are consistent with a delocalized species with considerable spin density at C_1 and C_3.[6] Experimentally, it is observed that alkynes are formed as the major product in reactions of the propargyl–allenyl-type free radicals. Free-radical chlorination of propyne[7] or allene,[7] and 2-butyne,[8] produces only the propargyl chloride; tri-*n*-butyltin hydride reacts with propargyl chlorides to produce mixtures of alkyne and allene in which the former is always dominant;[9] in gas-phase radical combination reactions methyl radical reacts with 8 in one case to give a 1:1 mixture of butyne and 1,2-butadiene,[10] and in the other a 3.5:1 mixture.[11] Thus, the formation of *only* allene in the reactions of Grignard reagents with propargyl chlorides in the presence of Fe(III) is not consistent with a SET, free-radical process.

The formation of allenes in the catalyzed process is proposed to occur via the mechanism illustrated in Scheme I incorporating a catalytic cycle involving low valence state transition metal species similar to those proposed by Tamura and Kochi.[12] Although the scheme outlined is based on an Fe(III)–Fe(I) cycle, an Fe(II)–Fe(0) cycle is also possible in that Fe(II) is also an active catalyst. Because of the possible redox capabilities of the reaction system it cannot be unambiguously specified which couple is active in the catalytic cycle.[13] Similar catalytic cycles can be written for the other active transition metals involving Co(II)–Co(0), Ni(II)–Ni(0), and Cu(II)–Cu(0) cycles.

The oxidative insertion of Fe(I)Cl into the propargyl chloride can occur to produce the propargyl iron species (**9**), which then undergoes rearrangement to the allenyl tautomer **10**, or by insertion with concomitant rearrangement to form directly **10**. The observation that both alkyne and allene are formed in the reactions of **1** and 1-propynylcyclohexyl chloride with methylmagnesium iodide suggests that a direct oxidative insertion to form **9** occurs. The observation that as the degree of substitution at the propargyl carbon increases the reactivity of the propargyl chloride decreases is consistent with a steric effect on the rate of direct insertion to form **9**. Displacement of chloride in **9** or **10** by alkyl of the Grignard reagent produces the bisorganoiron species **11** and **12** which then decompose to alkyne or allene with regeneration of the low oxidation state metal species. Morrell and Kochi[14] have reported on the formation and thermal decomposition of a bisorganonickel(II) complex which would be similar to that formed in the Ni(II) catalyzed process reported herein. Evidence for the intermediacy of allenyl transition metal compounds such as **12** has been derived from studies on the reactions of dialkylcuprates with propargyl chlorides.[15]

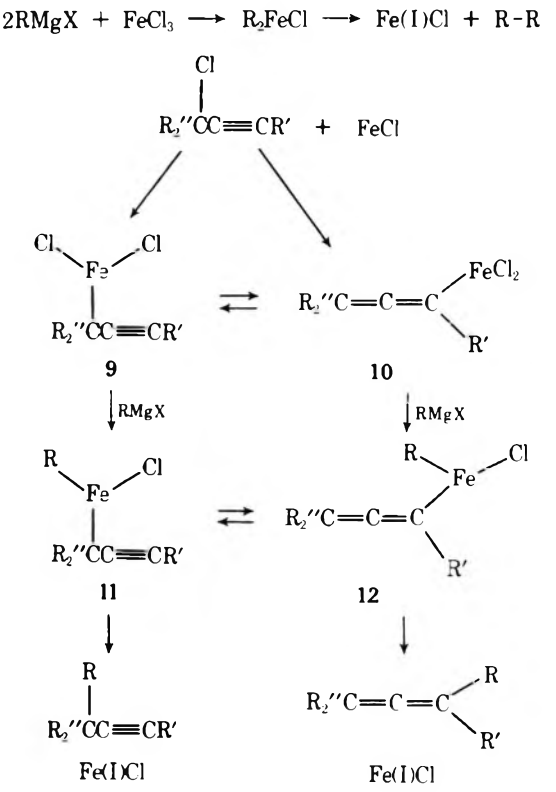
Whether tautomeric equilibrium is established between **9** and **10** and/or between **11** and **12** cannot be specified and must await the results of further studies. The exclusive formation of allene with the primary and secondary alkyl Grignard reagents can be attributed to a steric effect on the tautomeric equilibrium between **11** and **12**.

The decreased reactivity of the secondary alkyl Grignard reagents relative to the primary alkyl reagents, and the total lack of reactivity of *tert*-butylmagnesium bromide, is probably due to increased steric effects in the displacement of chloride in **9** and/or **10** by the Grignard reagent.

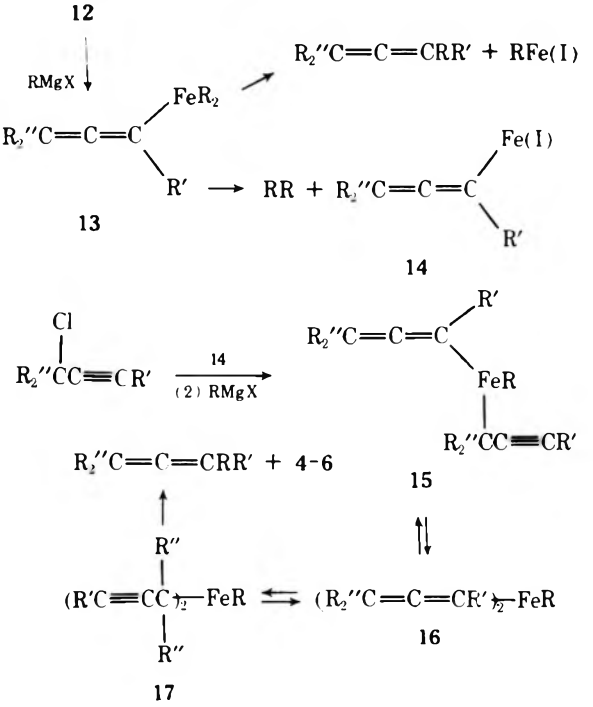
The formation of the minor products octane and the dimers **4–6** can be visualized as occurring via an extension of the mechanism in Scheme I to include trisorganometal species (Scheme II). Displacement of the remaining chloride in **12** would produce **13** which can decompose either to give allene and an alkyliron(I) species or to octane and the iron(I) species **14**. Oxidative insertion of **14** into the propargyl chloride forms the trisorganoiron species **15–17** which decompose to the dimers **4–6**. Decomposition of **13** must occur to approximately the same extent via the two pathways shown as evidenced by the similarity in yields of octane and the dimers.

Critical to the operation of the catalytic cycle is the rate of decomposition of the bisorganometal species similar to **11** and

Scheme I



Scheme II



12 in Scheme I. The decrease in catalytic activity in the sequence Fe > Co > Ni > Cu is probably due to the increasing stability of bisorganometal species on going from iron to copper.[16] The loss of catalytic activity in the nickel and copper systems when an excess of Grignard reagent is present suggests that some nickel or copper species is formed by reaction with the Grignard reagent which is not capable of entering the catalytic cycle. The lack of catalytic activity by chromium, maganese, rhodium, and silver must also be due to greater stability of the alkylmetal species.[17,18] Further studies must be carried out to clarify this point.

It is interesting to compare the catalytic activity described herein with that reported by Tamura and Kochi for the iron,[12a] copper,[12b] and silver[12c] catalyzed reactions of Grignard reagents with alkyl and vinyl halides. Silver catalyzes the coupling of Grignard reagents with alkyl halides via a free-radical pathway.[12c] Copper catalyzes coupling via a nonradical pathway, as well as disproportionation.[12b] Iron catalyzes disproportionation with alkyl halides and coupling with vinyl halides.[12a] In the present work silver as a catalyst was ineffective, while both iron and copper catalyzed coupling, but not disproportionation. This unique catalytic reactivity must be due to the presence of the C≡C. The presence of an adjacent C=C or aromatic ring does not result in coupling with these catalysts.

Although many studies have indicated that the addition of cobalt chloride to Grignard reagents induces free-radical reaction,[19] the evidence presented herein indicates that such reactions need not necessarily proceed via free-radical mechanisms. For example, Coulomb-Delbecq and co-workers have suggested very recently that the reactions of propargylic acetates with methylmagnesium iodide in the presence of cobalt chloride to produce allenes occur via a free-radical process.[20] It is critical to note that no alkynes are formed, and thus it is very doubtful if a free-radical process is involved in those reactions.

Experimental Section

Iron(III) Catalyzed Reaction of 4-Chloro-4-methyl-2-pentyne (1) with *n*-Butylmagnesium Bromide. To a solution of 5 g (0.067 M) of 1 in 50 mL of ether, to which has been added 5.0 mL of 5×10^{-6} M ferric chloride or ferric acetonylacetonate in tetrahydrofuran, maintained at 0 °C under a helium atmosphere is added 2 molar equiv[21] of 0.5 M *n*-butylmagnesium bromide in ether.[22] The reaction mixture was hydrolyzed by the addition of 5 mL of water. The organic layer was decanted from the aqueous phase, dried ($MgSO_4$), and the solvent removed by distillation. Analysis by GLPC on a 10-ft Carbowax 20M on firebrick column indicated the presence of two short retention-time peaks and four longer retention-time peaks. The six components were isolated by preparative GLPC and identified as octane (≤5%), 2-methyl-2,3-octadiene (90%), dimers **4**–**6** (total ~4%) and an apparently rearranged dimer (~1%) by high-resolution mass spectrometry and NMR. **4**: m/e 162; NMR ($CDCl_3$) δ 1.56 (s, 12 H) and 1.67 (s, 6 H). **5**: *m/e* 162; NMR ($CDCl_3$) δ 1.27 (s, 12 H) and 1.80 (s, 6 H). **6**: *m/e* 162; NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.66 (s, 6 H), 1.77 (s, 3 H), and 1.30 (s, 3 H). Unknown dimer: *m/e* 162; NMR ($CDCl_3$) δ 1.47 (s), 1.55 (s), 1.81 (s).

General Procedure for Transition Metal Catalyzed Reactions of Propargyl Chlorides with Grignard Reagents. The quantities and procedure outlined above were employed as standard reaction conditions. The optimum rates of addition of the Grignard reagent to the chloride–catalyst solution were determined in preliminary runs by monitoring the extent of reaction by GLPC techniques. Optimum addition times are given in Table I. The product mixtures were analyzed by GLPC and the yields were calculated using an internal standard. The allenes were purified by preparative GLPC[23] and characterized by high-resolution MS and NMR. All of the substituted allenes prepared in this study have been reported previously in the literature.

Competitive Reactivity Experiments. All competitive reactivity experiments were carried out in the following manner. To 1:1 molar mixtures of the two substrates in ether (1 M) containing the appropriate concentration of the catalyst was added, in portions, a total of 0.5 molar equiv of the Grignard reagent. After addition of the portions of the Grignard reagent an aliquot of the reaction mixture was removed, hydrolyzed, and analyzed by GLPC. Product identification was carried out by comparison of retention times with the products derived on reaction of each of the substrates individually.

Registry No.—**4**, 17553-34-3; **5**, 17553-33-2; **6**, 65150-08-5; butyl bromide, 109-65-9; *sec*-butyl bromide, 78-76-2; ethyl iodide, 75-03-6; methyl iodide, 74-88-4; isopropyl bromide, 75-26-3; *tert*-butyl bromide, 507-19-7.

References and Notes

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(13) See also ref 12a.
(14) D. G. Morrell and J. K. Kochi, *J. Am. Chem. Soc.*, **97**, 7267 (1975).
(15) See accompanying article on the reactions of dialkylcuprates with propargyl chlorides [D. J. Pasto, S.-K. Chou, E. Fritzen, R. H. Shults, A. Waterhouse, and G. F. Hennion, *J. Org. Chem.*, following article in this issue].
(16) Attempts to prepare alkyl- and aryliron compounds indicate that such species undergo decomposition at low temperatures (see M. Tsutsui, *Ann. N.Y. Acad. Sci.*, **93**, 133 (1961)). An alkylarylnickel(II) complex has been prepared and its decomposition studied (see ref 14). Alkylcopper compounds are well known.
(17) Trimethylchromium has been prepared in ether solution and is reasonably stable at 0 °C (K. Claus and C. Beermann, *Angew. Chem.*, **71**, 627 (1959)). Dimethylmanganese has also been prepared and is stable in ether at 0 °C but explodes when dry at higher temperatures (C. Beermann and K. Clauss, *Angew. Chem.*, **71**, 627 (1959)).
(18) Alkyl and aryl derivatives of second row transition metals have been prepared and show reasonable stability (see J. Chatt and B. L. Shaw, *J. Chem. Soc. A*, 1836 (1966), and references contained therein).
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(21) The use of 50–100% excess of the Grignard reagent results in the maximum yield of allene.
(22) GLPC analysis immediately after completion of the addition of the Grignard reagent showed that the reaction had gone to completion.
(23) Purification of the more highly substituted allenes by distillation must be carried out at pot temperatures below 100 °C in order to avoid cyclodimerization and rearrangement of the allenes to conjugated dienes. The injection port, detector block, and column must be kept below 150 °C during preparative GLPC isolation procedures.

Allene Formation in Reactions of Propargyl Chlorides with Dialkylcuprates and Alkylallenylcuprates[1]

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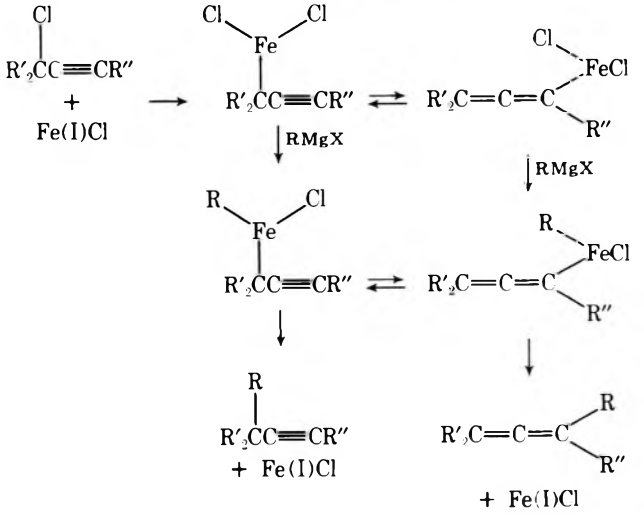
Dialkylcuprates react with propargyl chlorides to form allenes in generally excellent yield. The mixed *n*-butylmethyl- and *tert*-butylmethylcuprates react to preferentially transfer the *n*-butyl (67:29) and *tert*-butyl (97:3) groups, the latter providing an excellent means for the synthesis of *tert*-butylalleres. Small amounts of coupled product derived from the dialkylcuprates are formed, along with allene formally derived by net reduction of the propargyl chloride. It is shown that the "reduced" allene is formed by hydrolysis of an allenylcopper(I) compound formed during the reaction. Allenylcopper(I) compounds, alkylallenylcuprates, and bisallenylcuprates were prepared and their chemistry was explored in a preliminary manner. Reaction of alkylallenylcuprates with an alkyl halide produced alkane only, while reaction with propargyl chlorides resulted in the formation of only allenes. These reactions are compared with those of dialkylcuprates with alkyl halides and tosylates and the mechanisms of the reactions are discussed.

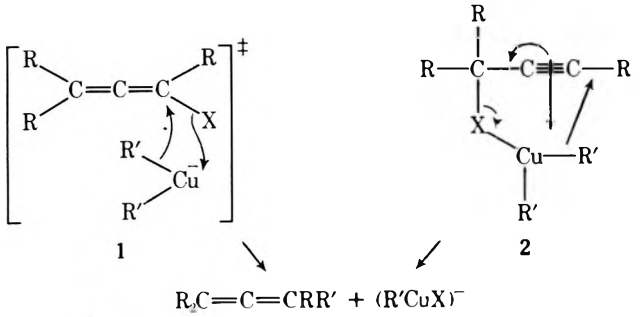
Introduction

In the preceding articles we have described the results of studies of the noncatalyzed[2] and transition metal catalyzed[3] reactions of propargyl chlorides with Grignard reagents. In the transition metal catalyzed process, allene formation was proposed to occur via a catalytic cycle in which a low-valence state metal species, formed by reaction of the metal salt (illustrated below with ferric chloride) with the Grignard reagent, undergoes insertion into the carbon–chlorine bond of the propargyl chloride to produce an equilibrium mixture of propargyl and allenyl metal derivatives. Displacement of the chloride bonded to the metal by an alkyl group produces a bisorganometal species which undergoes thermal decomposition to produce allene and regenerate the low-valence state metal species. Only when the alkyl group of the Grignard reagent is methyl and the propargyl chloride is not terminal is there an appreciable amount of the alkyl propargyl metal species present which undergoes decomposition to form alkyne. In all other cases only allene is formed. Transition metals found to be active at 5×10^{-5} M are Fe(III), Fe(II), Co(II), Ni(II), Cu(II), and Cu(I).

$$RMgX + FeCl_3 \longrightarrow R_2FeCl \longrightarrow RR + Fe(I)Cl$$

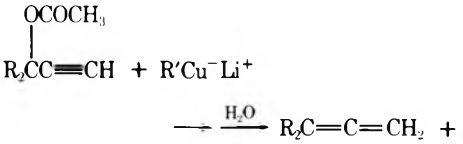


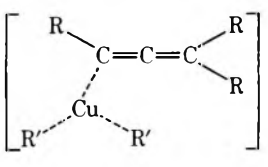
In view of the catalytic activity of Cu(II) and Cu(I) and the nature of the mechanism proposed, we decided to extend our investigations to the stoichiometric reactions of dialkylcuprates with propargyl chlorides, an area where only limited work had been carried out previously. Landor and co-workers[4] have reported that allenyl and propargyl halides react with dialkylcuprates to form allenes. These authors proposed that the allenyl halides react via a four-centered transition state (**1**), while the propargyl halides react via a π complex (**2**) which decomposes to allene with rearrangement of a π bond.



$$R_2C{=}C{=}CRR' + (R'CuX)^-$$

Crabbé and co-workers have reported that the reaction of propargyl acetates with dialkylcuprates produce allenes and proposed that the reactions proceeded via an S_N2' mechanism.[5] During the course of our investigation, Crabbé and co-workers reported that when the reaction of propargyl acetates with dialkylcuprates is carried out at low temperature and hydrolyzed immediately, a considerable amount of "reduced" allene is formed.[6] Based on these observations, Crabbé proposed formation of an intermediate represented as **3** which can undergo decomposition to produce allene, or be intercepted by hydrolysis to produce reduced allene.





3

In this article we describe the results of our studies on the synthetic aspects of the reaction of homo and mixed dialkylcuprates with propargyl chlorides, and on the preparation and reactions of alkenyl-containing cuprates.

Results

Reaction of lithium di-*n*-butylcuprate (**4**) with 3-chloro-

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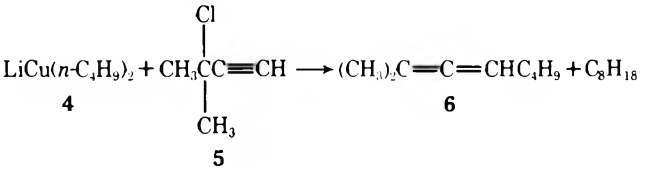
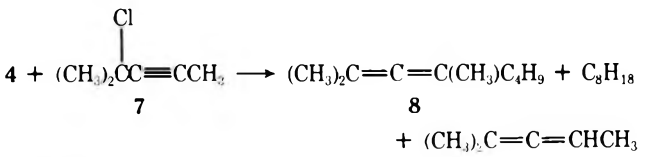
3-methyl-1-butyne (**5**) at −78 °C followed by hydrolysis produces 2-methyl-2,3-octadiene (**6**) along with a low yield of

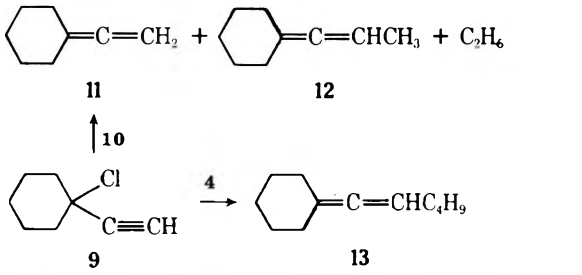


octane. In a similar manner **4** reacts with **7** at −78 °C to produce **8** along with octane and trimethylallene. At 0 °C, the reaction is very fast but the yield of **8** is lower, while the yield



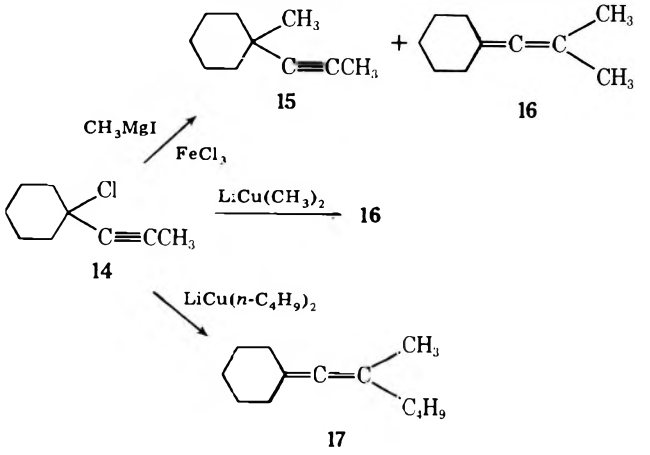
of trimethylallene is increased. Although **4** undergoes only very slow decomposition to give octane at −78 or 0 °C, monobutylcopper(I) undergoes decomposition to octane considerably faster. A comparison of the rate of formation of octane by decomposition of monobutylcopper(I) with that during the reaction of **4** with **7** shows that octane must be formed during the reaction of **4** with **7** (see Experimental Section). Monitoring the reaction with time shows that the yield of trimethylallene increases to a maximum and then decreases owing to decomposition of the allenylcopper(I) species formed in the reaction (vide infra).

The reaction of 1-chloroethynylcyclohexane (**9**) with lithium dimethylcuprate (**10**) produces the "reduced" allene **11**



and 1-propenylidenecyclohexane (**12**) in a 1:4 ratio. A reaction mixture of **9** with **10** was maintained at −78 °C and aliquots were periodically removed, hydrolyzed, and analyzed by GLPC. The ratio of **11**:**12** remained constant although at room temperature slow decomposition occurred resulting in lower yields of **11**. Deuteriolysis of a reaction mixture derived from **9** and **10** produced **11** containing 1.0 deuterium atom at the allenyl position. During the reactions of **9** with **10** gas evolution occurred. A sample of the gas above a reaction mixture was analyzed by mass spectrometry showing the presence of ethane.

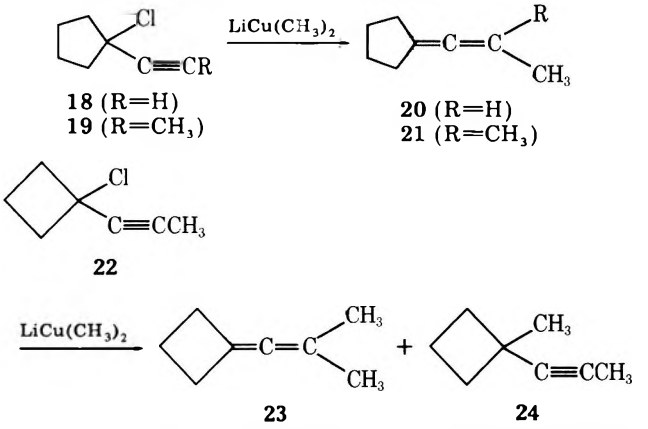
In contrast to the reaction of **9** with **10**, the reaction of **9** with



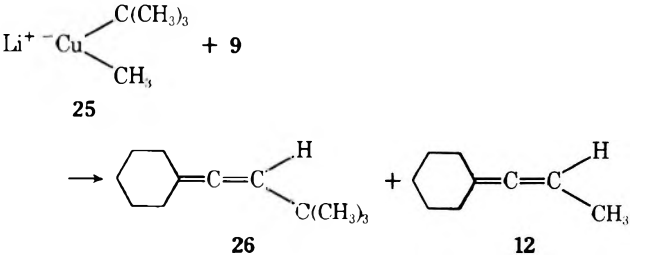
di-*n*-butylcuprate (**4**) produces only the alkylated allene **13**. Only traces of octane are formed, and the reduced allene **11** could not be detected.

Although 1-(1-propynyl)cyclohexyl chloride (**14**) reacts with methylmagnesium iodide in the presence of ferric chloride to produce a 1:1 mixture of 1-(1-propynyl)methylcyclohexane (**15**) and (2-methyl-1-propenylidene)cyclohexane (**16**),[2] **14** reacts with **10** to form only **16**. No reduced allene of **14** was formed. In a similar manner **14** reacted with **4** to produce **17**.

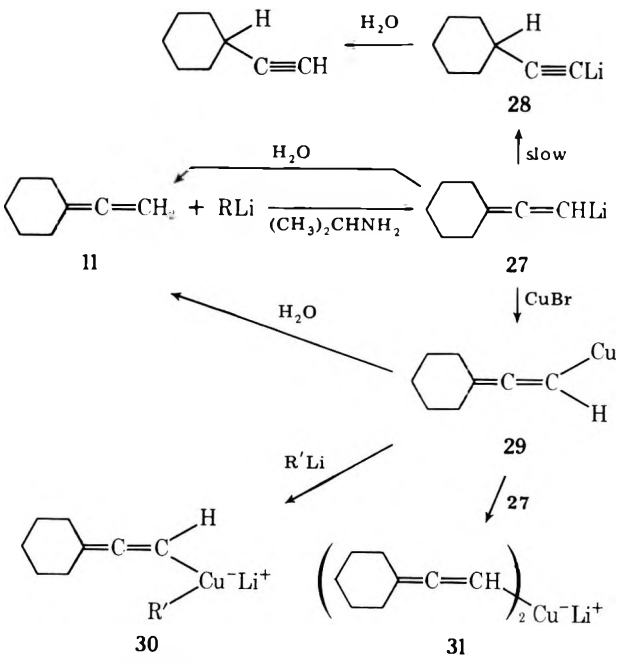
Application of the reaction to the alkynylcyclopentyl and cyclobutyl chlorides provided interesting contrasts in both reactivity and mode of reaction. The cyclopentyl derivatives **18** and **19** reacted considerably slower than **9** and **14**, **18** requiring 18 h for completion. In both cases only the methylated allenes **20** and **21** were formed. The cyclobutyl derivative **22** underwent very slow reaction with **10** to produce in low yield a 60:40 mixture of allene **23** and alkyne **24**.



In the transition metal catalyzed reaction of propargyl chlorides with Grignard reagents it was not possible to introduce a *tert*-butyl group onto the allene. We therefore investigated the possibility of transfer of a *tert*-butyl group from a mixed dialkylcuprate,[8] specifically lithium *tert*-butylmethylcuprate (**25**).[9] Reaction of ethynylcyclohexyl chloride (**9**) with **25** gave an 80% yield of a 97:3 mixture of the *tert*-butyl and methyl allenes **26** and **12**. Much lower selectivity is exhibited by lithium *n*-butylmethylcuprate, reacting with **9** to produce **13** and **12** in 67:29 ratio along with 3.2% of reduced allene **11**. Magnesium cuprates, prepared from alkylcopper and Grignard reagents,[9] failed to react with the propargyl chlorides.

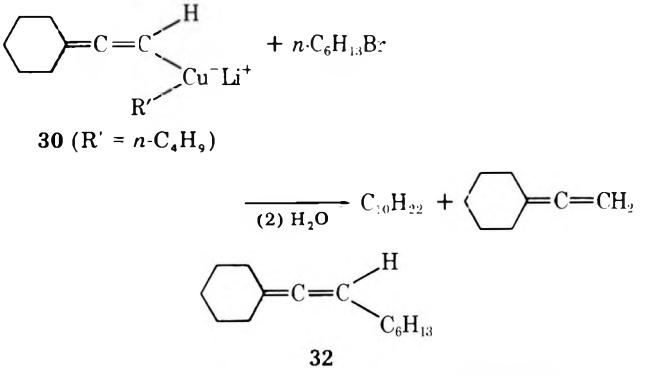


The formation of reduced allene in many of the instances described above and the formation of both allene and alkyne from **22** initially suggested that the propargyl–allenyl group becomes covalently bonded to the copper of the cuprate. In order to clarify this possibility we have prepared and studied in a preliminary manner the reactivity of allenylcopper(I) compounds and alkylallenyl- and bisallenylcuprates. Reaction of **11** with a methyllithium in the presence of a catalytic quantity of isopropylamine[10] at 0 °C rapidly produces the allenyllithium compound **27**. Immediate hydrolysis regenerates **11** uncontaminated by the isomeric alkyne. (If the solution of **27** is allowed to warm to room temperature for 30 min



extensive rearrangement to **28** occurs.[11] Addition of the solution of **27** to a suspension of cuprous bromide in ether produces an insoluble dark reddish-brown precipitate of **29**. Hydrolysis of **29** produces *only* allene **11**. The allenylcopper compound **29** appears to be quite stable in ether at room temperature. Addition of 1 molar equiv of an alkyllithium produces the mixed cuprate **30**, while addition of a second molar equiv of **27** produces the bisallenylcuprate **31**. Both **30** and **31** produce only **11** on hydrolysis.

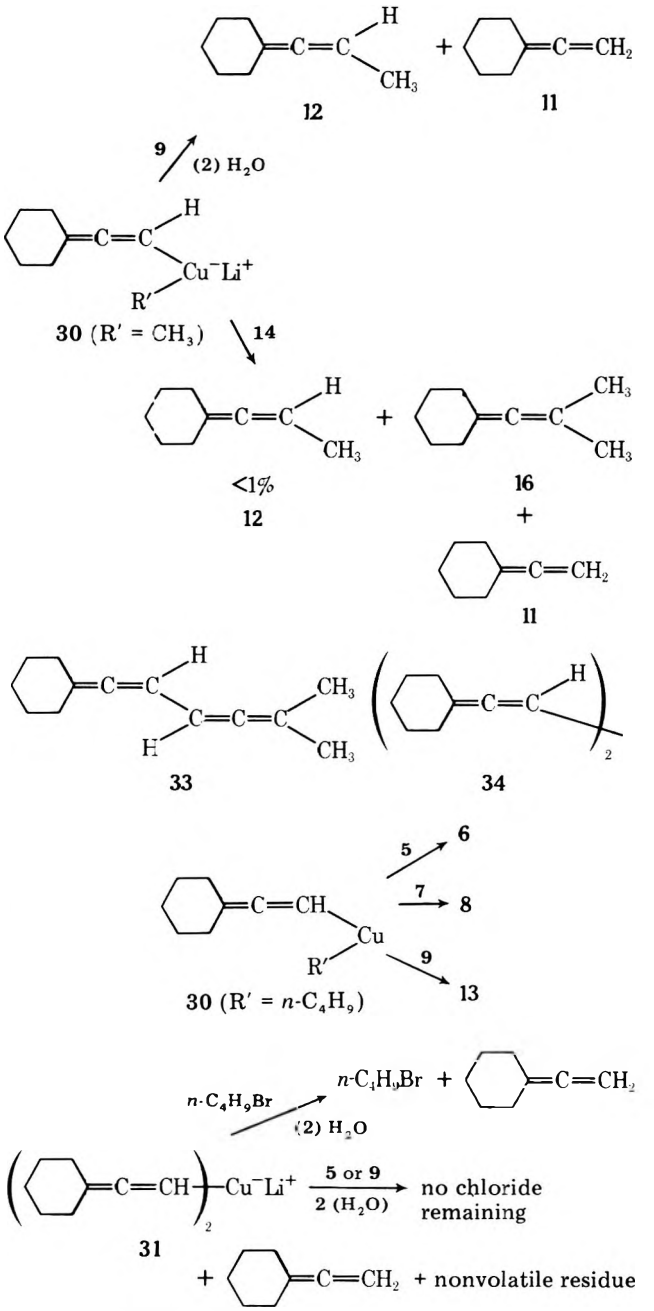
Reaction of **30** (R′ = $-n$-C_4H_9) with n-hexyl bromide followed by hydrolysis produced decane (80%) and allene **11**. No butyl- or hexylallene (**13** and **32**) could be detected.



Reaction of **30** (R′ = $-CH_3$) with propargyl halide **9** produced an excellent yield (>80%) of **16**, along with **11** formed during hydrolysis. Reaction of **30** (R′ = $-CH_3$) with **14** gave **16**. Careful GLPC analysis indicated the possible presence of a very small amount (<1%) of **12**. Whether **12** is formed by methyl transfer to the allenyl portion in **30** (R′ = CH_3) or by hydrolysis of an allenyl fragment attached to copper derived from **14** could not be determined. The other data presented herein, however, would suggest that the **12** is formed via the latter pathway. In neither case was any of the bisallenes **33** or **34** formed.

Similar results are obtained in reactions of **30** (R′ = n-C_4H_9) with propargyl halides **5**, **7**, and **9**, producing only the butylated allenes **6**, **8**, and **13** derived from the propargyl chlorides. In none of these reactions was any bisallene detected.

Reaction of the diallenylcuprate **31** with n-butyl bromide for 30 min at room temperature resulted in no apparent reaction. GLPC analysis after hydrolysis showed the presence of unreacted n-butyl bromide and allene **11**. Reaction of **31** with **5** at 0 °C led to the complete disappearance of **5**, yet none



of the bisallene **33** could be detected. Hydrolysis of the reaction mixture resulted in the formation of allene **11** with ~70% recovery. Considerable noncharacterizable residue remained after removal of **11**. Similarly, reaction of **31** with **9** resulted in the disappearance of the propargyl halide, yet GLPC analysis after hydrolysis showed the formation of **11** (70%, recovery) and no bisallene. Evaporation of **11** again left considerable noncharacterizable residue. These reactions of bisallenylcuprates are under further scrutiny.

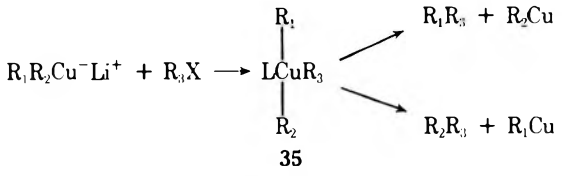
Discussion

The results reported herein differ in several aspects from those reported previously for reactions of dialkylcuprates with alkyl halides and tosylates. Mandeville and Whitesides[8] have reported that reactions of mixed dialkylcuprates with an alkyl halide result in coupling of only the alkyl groups attached to copper to the alkyl group of the halide. No coupling products derived from the two alkyl groups attached to the copper are formed. In the reactions of dialkylcuprates with propargyl halides, coupling of the alkyl groups attached to copper does occur.

$$R_1R_2Cu^-Li^+ + R_3Hal \rightarrow R_1R_3 + R_2R_3 \ (no\ R_1R_2)$$

Mandeville and Whitesides[8] have also correlated rates of reactions of dibutylcuprate with alkyl halides with other typical S_N2 displacement reactions and suggest that the dialkylcuprate reactions occur via "unexceptional S_N2" pathways; however, distinction between attack by copper or an alkyl anion could not be made.

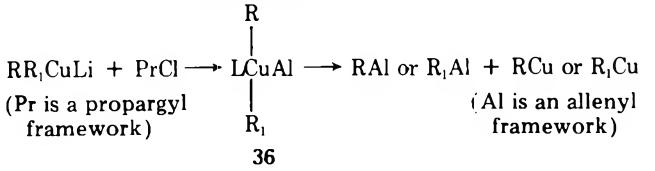
On the basis of Mandeville and Whitesides'[8] and earlier results, and the results of reactions of dialkylcuprates with alkyl tosylates, Johnson and Dutra[12] suggested that the mechanism of coupling involved formation of a square-planer Cu intermediate in which the alkyl groups attached to the Cu are trans located. Rapid decomposition before rearrangement results in coupling of only groups which are cis located.



35

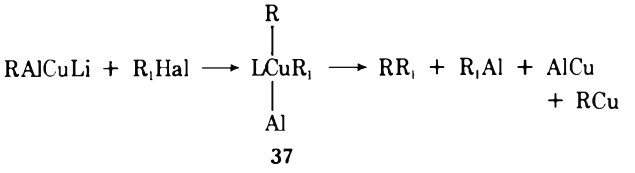
(L is a liganded solvent molecule)

The results of the present study cannot be accommodated by such a mechanism. Assuming that the groups attached to copper become trans-located intermediates **36–39** would have

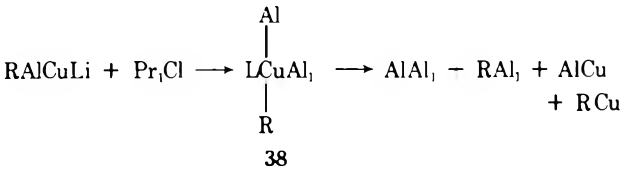


(Pr is a propargyl framework) (Al is an allenyl framework)

36



37



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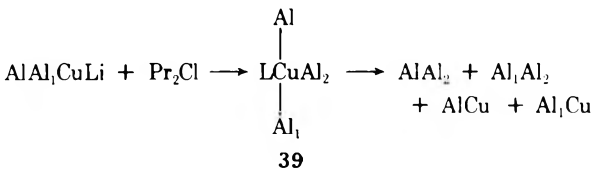
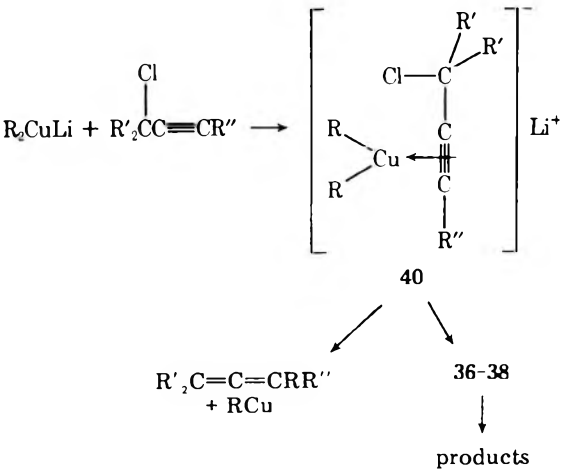


39

been formed. Coupling of cis-located groups would have produced only those products shown. However, intermediate **36** produced not only allene, but also alkane; **37** gave alkane and no allene, **38** gave only allene RAl_1 and no bisallene or RAl, while **39**, if formed, did not give any coupled bisallenes. Obviously these results are not consistent with the Johnson and Dutra mechanism. It is also obvious that when an allenyl group is bonded to the copper it is not capable of being coupled with an alkyl or propargyl halide, being similar in reactivity with an alkynyl group attached to copper.

In view of the above, we believe that allenes are not formed via the intermediates **36** and **38**, but arise by alkyl transfer from copper to the propargyl halide in a π-type complex (**40**). In general, allene is formed except when the allene contains considerable strain energy as in the case of the reaction with **22** where alkyne is also formed. In competition with alkyl transfer to the propargyl halide, nucleophilic attack by Cu to produce **36–39** must also occur. Competition between nucleophilic attack by alkyl and copper must be controlled by the nucleophilicity of the alkyl group attached to the Cu. This feature of the reaction is under further study. If groups must be cis related to couple, an intermediate such as **36** must be sufficiently stable to undergo rearrangement to **37** prior to decomposition.



40

In a recent article, Pearson and Gregory[13] proposed that the structure of lithium dimethylcuprate is that shown as **40.** These authors favor a rate-determining oxidative addition with inversion followed by a rapid reductive elimination with retention of configuration, all occurring within a dimeric species. Although the reaction involves reaction between a dimeric cuprate and organic halide or tosylate, no evidence is available indicating whether the dimeric species remains intact or forms intermediates of the type suggested by Johnson and Dutra. Regardless, the Pearson and Gregory mechanism is not consistent with the results of our present study for the reactions of dialkylcuprates with propargyl chlorides.

As in the previous article describing the transition metal catalyzed formation of allenes in the reactions of Grignard reagents with propargyl halides,[2] special reactivity is attributed to the presence of the C≡C. We currently believe that the mechanisms of the two reactions differ, in the former a covalent carbon–metal bond being formed and the latter occurring via a π complex.

Experimental Section

General Procedure for the Preparative Reactions of Propargyl Chlorides with Lithium Dialkylcuprates 4 and 10. To a solution of 5 mmol of lithium di-*n*-butylcuprate (**4**) [prepared at −78 °C by the addition of 10 mmol of *n*-butyllithium in hexane to a suspension of 5 mmol of cuprous bromide in hexane (10 mL)] or lithium dimethylcuprate (**10**) (prepared at −78 °C from 10 mmol of methyllithium and 5 mmol of cuprous bromide suspended in 10 mL of ether) under a helium atmosphere at 0 °C was added 2.5 mmol of propargyl chloride in 5 mL of ether. The reaction mixtures were stirred at 0 °C for 30 min and were hydrolyzed by the addition of 2 mL of water. The organic layer was decanted and the aqueous layer extracted with 10 mL of ether. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed by fractional distillation. The reaction mixtures were analyzed and separated by GLPC and the products were characterized by NMR and MS. Products and yields are given in Table I.

In the case of reaction of **10** with **9** a sample of the gas above the reaction mixture was removed in an evacuated MS sampling bulb. High-resolution MS analysis showed the presence of large amounts of ethane: *m/e* for C_2H_6 calcd 30.0470; found 30.0468.

All allenes formed in this study have been characterized previously except the following.

13: NMR ($CDCl_3$) δ 1.12 (distorted t, 3 H), 1.45–1.78 (bm, 10 H), 1.78–2.45 (bm, 6 H), 4.85 (bm, 1 H); MS calcd for $C_{12}H_{20}$ 164.1565, found 164.1570.

26: NMR (CCl_4) δ 1.01 (s, 9 H), 1.42–1.83 (bm, 6 H), 1.9–2.4 (bm, 4 H) 5.95 (p, 1 H); MS calcd for $C_{12}H_{20}$ 164.1565, found 164.1568.

23: NMR ($CDCl_3$) δ 1.66 (s, 6 H), 1.68 (p, J = 7.5 Hz, 2 H), 2.93 (t, J = 7.5 Hz, 4 H); MS calcd for C_8H_{12} 108.0939, found 108.0940.

Table I. Reactions of Dialkylcuprates with Propargyl Chlorides

Dialkylcuprate	Registry no	Propargyl chloride	Registry no.	Products (%)
4	24406-16-4	**5**	1111-97-3	**6** (60)
4		**7**	999-79-1	**8** (60–65), $(CH_3)_2C{=}C{=}CHCH_3$ (~15)
4		**9**	6209-75-2	**13** (90)
4		**14**	60820-36-2	**17** (75)
10	15681-48-8	**9**		**12** (70), **11** (20)
10		**14**		**16** (70)
10		**18**	40185-07-7	**20** (20)
10		**19**	65149-99-7	**21** (50)
10		**22**	65150-00-7	**23** (12), **24** (8)
25	58096-49-4	**9**		**26** (85), **12** (2.5)
$(n\text{-}C_4H_9)(CH_3)Cu^-Li^+$	42278-64-8	**9**		**13** (42), **12** (28)

24: NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.83 (s, 3 H), 1.50–2.25 (m, 6 H); MS calcd for C_8H_{12} 108.0939, found 108.0941.

Reaction of 7 with 4. To a solution of 2.2 mmol of **4** in 3 mL of hexane at −78 °C under a helium atmosphere containing toluene as a GLPC internal standard was added 2.2 mmol of **7** in ether. Aliquots were periodically removed, hydrolyzed, and analyzed by GLPC. Aliquots were removed after 40 and 90 min, hydrolyzed, and analyzed by GLPC. The yields of products were at 40 min 18.6% octane, 3.3% trimethylallene, and 19.3% **8**, and at 90 min 51.9% octane, 15.2% trimethylallene, and 34.5% **8**. After 150 min the field of **8** approached 65%.

In a similar reaction maintained at 0 °C yields were after 5 min 42.9% octane, 18.5% trimethylallene, and 33% **8**, after 10 min 53.5% octane, 23.0% trimethylallene, and 37.8% **8**, and after 60 min 77.1% octane, 15.6% trimethylallene, and 40.8% **8**.

Measurement of Rate of Decomposition of *n*-Butylcopper(I) at −78 °C. *n*-Butylcopper(I) was prepared by the addition of 1 mmol of *n*-butyllithium in hexane to 1.0 mmol of cuprous bromide suspended in 2 mL of hexane at −78 °C containing 35 mg of toluene as a GLPC internal standard. The reaction mixture was maintained at −78 °C and aliquots were periodically removed, hydrolyzed, and analyzed by GLPC. The yields of octane are at 5 min 5.6%, 1 h 9.5%, and at 3 h 21.1%.

Deuteriolysis of Reaction Mixture of 9 with 10. To a solution of 1 mmol of **10** in 2 mL of ether at −78 °C was added 1 mmol of **9** in 2 mL of ether. The reaction mixture was stirred at −78 °C for 30 min and 1 mL of deuterium oxide was added. The reaction mixture was allowed to warm to room temperature and the organic layer was decanted, washed with water, and dried ($MgSO_4$). The **11** was isolated by preparative GLPC on a 10-ft Carbowax 20 M column at 150 °C. The NMR spectrum showed δ 1.55 (bm, 6 H), 2.2 (bm, 4 H), and 4.55 (m, 1 H). The mass spectrum was identical with that of **11** except the peaks in the parent ion region were at 1 amu higher; *m/e* calcd for $C_8H_{11}D$ 109.1002, found 109.1000.

Preparation and Hydrolysis of 27.[10] To 0.2 g (1.85 mmol) of **11** at 25 °C containing 40 mg of diisopropylamine was added 1.8 mmol of *n*-butyllithium in hexane. The NMR spectrum of the resulting solution (methyllithium in ether) showed a new resonance at δ 4.9 (m). Hydrolysis of an aliquot produced only **11**. Deuteriolysis produced **11** containing one deuterium (NMR and MS) at the allenyl position.

Hydrolysis and analysis of the reaction solution from above after stirring at 25 °C for 4 h showed the presence of ethynylcyclohexane and **11** in a 75:25 ratio.

Preparation and Hydrolysis of 29. To a solution 1.8 mmol of **27** in 1.0 mL of hexane at −78 °C was added 0.9 mmol of cuprous bromide. The reaction mixture was allowed to warm to −20 °C for 10 min resulting in the formation of a dark gray suspension. An aliquot of the reaction mixture was removed and hydrolyzed giving >95% recovery of **11**.

Preparation and Hydrolysis of 30. To the suspension of 1.8 mmol of **29** in hexane at −78 °C was added 1.1 mmol of RLi (R = CH_3 in ether or *n*-C_4H_9 in hexane) and the reaction mixture was allowed to warm to ~−20 °C for 10 min resulting in the formation of a very dark gray solution. Hydrolysis of an aliquot of the solution gave >95% **11**.

Reaction of 30 (R′ = *n*-C_4H_9) with 1-Bromohexane. To a solution of 1.0 mmol of **30** (R = *n*-C_4H_9) in 3 mL of hexane at 0 °C was added 1.0 mmol of 1-bromohexane. The reaction mixture was stirred at 0 °C for 30 min and hydrolyzed by the addition of 1 mL of water. The organic layer was removed, dried ($MgSO_4$), and analyzed by GLPC showing the presence of decane (80%) and **11**. No **13** or **32** could be detected by GLPC.

Table II. Reactions of 30 with Various Propargyl Chlorides

30, R	Propargyl chloride	Product[a] (yield)
CH_3	**9**	**12** (>80%)
CH_3	**14**	**16** (>80%)
n-C_4H_9	**5**	**6** (85%)
n-C_4H_9	**7**	**8** (90%)
n-C_4H_9	**9**	**13** (80%)

[a] **11**, formed by hydrolysis of **29**, was present in all cases.

Reaction of 30 with Various Propargyl Chlorides. To a solution of 1.0 mmol of **30** in 3 mL of ether or hexane at 0 °C was added 1.0 mmol of the propargyl chloride. The reaction mixture was stirred for 30 min at 0 °C and hydrolyzed with 1 mL of water. The organic layer was removed, dried ($MgSO_4$), and analyzed by GLPC. The results are given in Table II. No reduced allenes or bisallenes could be detected by GLPC.

Preparation and Hydrolysis of 31. To a solution of 0.3 g (2.78 mmol) of **11** at 0 °C was added 2.0 mmol of methyllithium in ether. After stirring at 25 °C for 10 min, the solution of **27** was chilled to −78 °C and 1.0 mmol of cuprous bromide was added giving a dark green solution. The reaction mixture was allowed to warm to 0 °C giving a very dark solution. Hydrolysis of an aliquot of the solution and analysis by GLPC showed the presence of only **11**.

Attempted Reaction of 31 with 1-Bromobutane. To a solution of 1.0 mmol of **31** at 0 °C was added 1.0 mmol of 1-bromobutane and the reaction mixture stirred at 0 °C. Aliquots were periodically removed, hydrolyzed, and analyzed by GLPC showing only the presence of **11** and 1-bromobutane.

Attempted Reaction of 31 with 5 and 9. To a solution of 1.0 mmol of **31** at 0 °C were added 1.0 mmol of **5** and **9**. Aliquots taken immediately after the addition of **5** and **9** showed the complete consumption of **5** and **9**, but no bisallenes **33** or **34** could be detected by GLPC.[14] Allene **11** was formed on hydrolysis. Hydrolysis of the reaction mixtures followed by separation of the organic phase, drying ($MgSO_4$), and removal of the solvent gave considerable quantities of nonvolatile residues which were not further investigated.

Registry No.—**11**, 5664-20-0; **13**, 20023-45-4; **23**, 65150-01-8; **24**, 65150-02-9; **26**, 59643-61-7; **27**, 65150-03-0; **29**, 65150-04-1; **30** (R = Bu), 65150-22-3; **30** (R = Me), 65150-23-4; **31**, 65150-24-5; 1-bromohexane, 111-25-1.

References and Notes

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(14) Bisallenes were easily detected and isolated by GLPC techniques in the previous article.[3]

Synthesis of Highly Branched, β-Arylated Nitroparaffins[1]

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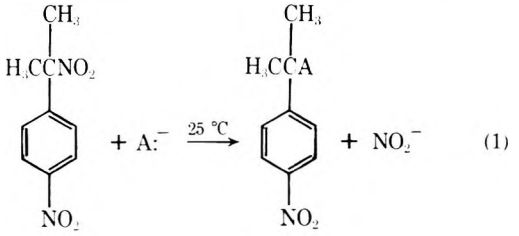
A synthetically useful one-step procedure for converting α-arylated tertiary nitro compounds into highly branched β-arylated nitroparaffins is described. These reactions appear to proceed via a chain mechanism in which radical anions and free radicals are intermediates.

Ten years ago it was discovered that the aliphatic nitro group of α,*p*-dinitrocumene (**1**) is readily displaced by a wide variety of nucleophiles as is shown in eq 1.[2] A large body of



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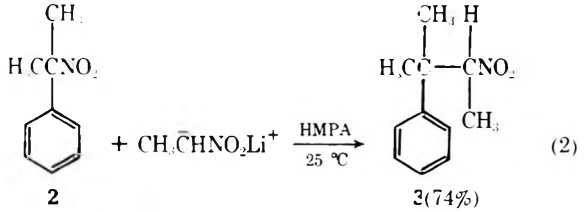
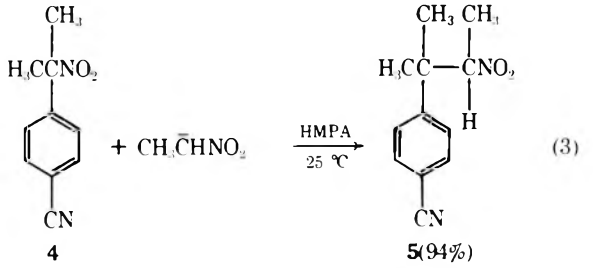
evidence now exists in support of the view that these are electron-transfer processes in which radical anions and free radicals are intermediates.[3] When the chemistry of α,*p*-dinitrocumene (**1**) was first described it was emphasized that the *p*-nitro group facilitates the displacements of eq 1; in no instance did α-nitrocumene (**2**) react with nucleophiles under conditions which resulted in complete reaction when α,*p*-dinitrocumene was employed.[2]

We have now found that the aliphatic nitro group of α-nitrocumene (**2**), and of substituted α-nitrocumenes and homologues thereof, can be displaced by nitroparaffin salts, albeit at a distinctly slower rate than when α,*p*-dinitrocumene is used. What is required is the use of hexamethylphosphoramide (HMPA) as the solvent, rather than the DMF or Me_2SO originally employed, and a relatively long reaction time (see Table I). Thus, in 45 h α-nitrocumene and the lithium salt of nitroethane react smoothly (eq 2). While the matter



2 **3**(74%)

has not been studied extensively, it appears that electron-withdrawing substituents facilitate these substitutions; for example, the reaction of eq 3 takes only 8 h and gives 94% yield. This type of reaction also proceeds at 25 °C when the salts of secondary nitroparaffins are employed. Table I summarizes our results; it should be noted that the yields given there refer to pure, isolated products.



4 **5**(94%)

Simple, synthetically useful methods for preparing α-arylated tertiary nitro compounds are now available.[4,5] Consequently, the facile one-step conversion of α-arylated nitro compounds into highly branched β-arylated nitroparaffins makes the latter readily accessible. Manifestly, the synthesis of the highly ramified nitro compounds of Table I by classical means would be a matter of some difficulty. The relative insensitivity to steric hindrance of the processes of Table I is consonant with the view that they are radical anion reactions (vide infra) and serves to emphasize, once again, the utility of radical anion reactions for the preparation of highly branched structures.[3]

Several of the transformations listed in Table I have been studied in regard to the matter of mechanisms; in each case the characteristics of electron transfer substitution processes have been observed. Thus, the reaction of the lithium salt of nitroethane with α-nitrocumene (**2**) requires 45 h to proceed to completion and produces pure 2-phenyl-2-methyl-3-nitrobutane (**3**) in 74% yield (eq 2). But if di-*tert*-butyl nitroxide is present at the 9 mol % level the reaction is completely inhibited for 45 h. *m*-Dinitrobenzene (20 mol %) also retards this reaction; after 45 h it proceeds only 4% to completion. *m*-Dinitrobenzene is recognized as a diagnostic for radical anions,[1] di-*tert*-butyl nitroxide is a free-radical scavenger[1,6,7] and clearly the reaction of eq 2 is a chain process.

Two reactions employing *p*-cyano-α-nitrocumene (**4**) have also been investigated. At 25 °C the transformation of eq 3 requires 8 h and gives a 94% yield of the pure β-arylated nitroparaffin **5**. In contrast, if di-*tert*-butyl nitroxide is present at the 10 mol % level there is no reaction after 8 h and 91% of the *p*-cyano-α-nitrocumene is recovered. Furthermore, *m*-dinitrobenzene (20 mol %) completely inhibits this reaction for at least 8 h.

The second reaction of *p*-cyano-α-nitrocumene which was studied from the standpoint of mechanism is shown in eq 4; after 50 h a 68% yield of the pure β-arylated nitro compound

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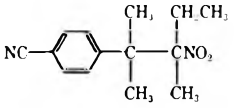
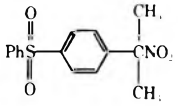
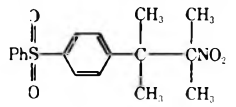
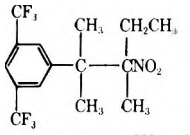
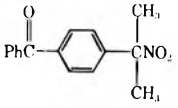
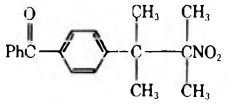
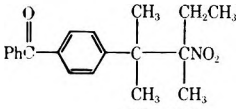
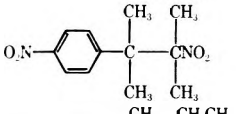
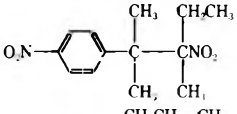
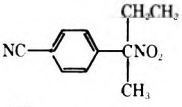
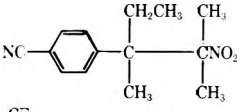
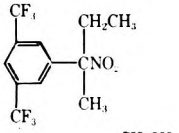
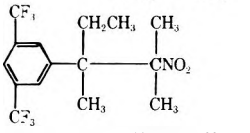
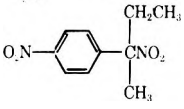
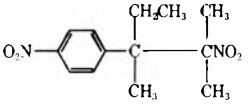
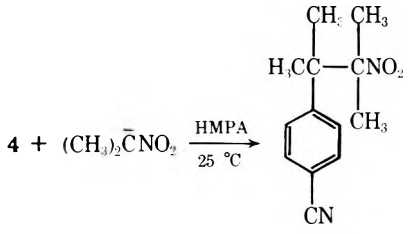
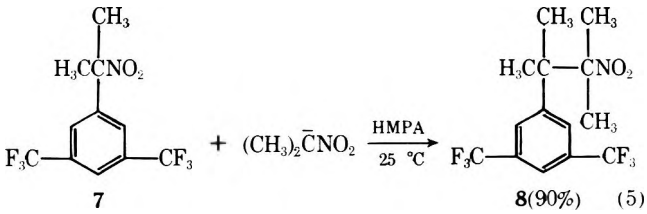
Table I. The Synthesis of β-Arylated Nitroparaffins at 25 °C[a]

α-Arylated nitro compd employed	Registry no.	Nitroparaffin salt employed	Registry no.	Reaction time, h	Product	Registry no.	% yield[b]
2	3457-58-7	$CH_3\bar{C}HNO_2Li^+$	28735-55-9	45	3	65253-35-2	74
4	58324-82-6	$CH_3\bar{C}HNO_2Li^+$		8	5	65253-36-3	94
4		$(CH_3)_2\bar{C}NO_2Li^+$	12281-72-0	50	6	65253-37-4	68
4		$CH_3CH_2\bar{C}(CH_3)Li^+$, NO_2	35818-95-2	46		65253-38-5	68
	58324-84-8	$(CH_3)_2\bar{C}NO_2Li^+$		110		65253-39-6	71
7	58324-86-0	$(CH_3)_2\bar{C}NO_2Li^+$		16	8	65338-72-9	90
7		$CH_3CH_2\bar{C}(CH_3)Li^+$, NO_2		45		65253-40-9	50
	58324-79-1	$(CH_3)_2\bar{C}NO_2Li^+$		72		65253-41-0	62
"		$CH_3CH_2\bar{C}HLi^+$, NO_2		74		65253-42-1	61
1		$(CH_3)_2\bar{C}NO_2Li^+$		2[c]		14851-03-7	84
1		$CH_3CH_2\bar{C}HLi^+$, NO_2		6		65253-43-2	74
	65253-33-0	$(CH_3)_2\bar{C}NO_2Li^+$		92		65253-44-3	60
	65253-34-1	$(CH_3)_2\bar{C}NO_2Li^+$		45		65253-45-4	60
	58324-83-7	$(CH_3)_2\bar{C}NO_2Li^+$		3		65253-46-5	76

[a] All reactions were carried out in HMPA at 25 °C with exposure to light.[14] [b] Pure, isolated product. [c] M. M. Kestner, Ph.D. Thesis, Purdue University, May 1973.



6(68%) (4)



8(90%) (5)

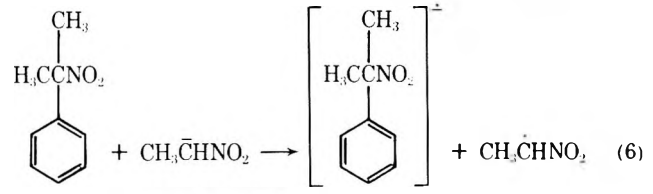
6 is isolated. As in the preceding cases, catalytic amounts of *m*-dinitrobenzene and di-*tert*-butyl nitroxide completely inhibit the reaction.

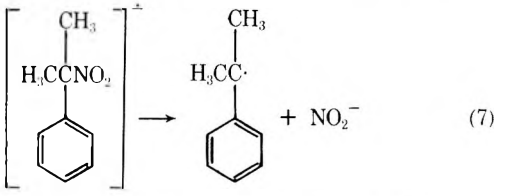
The process of eq 5 requires 16 h and gives a 90% yield of the β-arylated nitroparaffin 8. Here again complete inhibition is observed when *m*-dinitrobenzene (10 mol %) or di-*tert*-butyl nitroxide (8 mol %) are present; 98% of the initially employed α-nitrocumene 7 is recovered from the *m*-dinitrobenzene experiment and 85% from the one in which nitroxide is present.

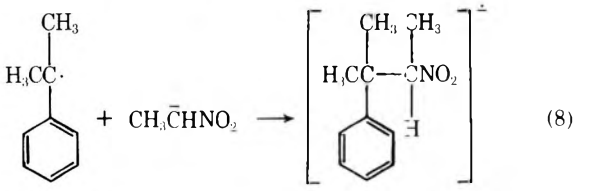
The effect of light on these reactions is also noteworthy. All the transformations of Table I are conducted with exposure to the illumination of two ordinary 20-W fluorescent lamps. However, when α-nitrocumene (2) and the lithium salt of nitroethane are brought together under conditions which result in the reaction of eq 2, except that now the system is maintained in total darkness, no reaction occurs and 83% of the

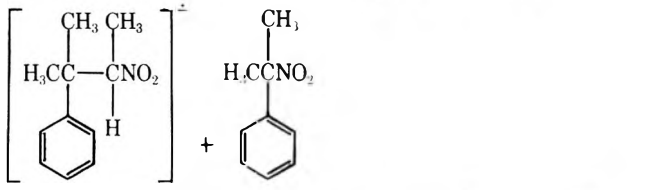
α-nitrocumene is recovered. Nor is this a unique result; the reactions of eq 3 and 4 also do not occur in the absence of light. And while the reaction of eq 5 does proceed in the dark it is unambiguously speeded up by light (cf. Experimental Section). Although many electron-transfer substitution reactions take place in the dark they are often accelerated by light.[1] The dramatic light effects observed in the reactions of α-nitrocumene and *p*-cyano-α-nitrocumene, and the smaller one noted in the reaction of eq 5, are consonant with an electron-transfer mechanism.

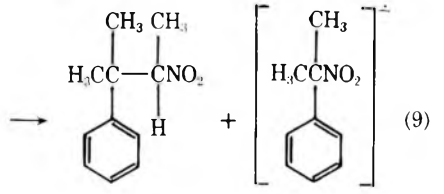
The chain mechanism of eq 6–9 provides a simple basis for


(6)


(7)

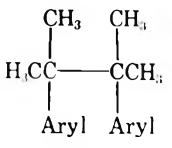

(8)

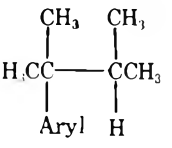



(9)

understanding the foregoing facts and is consistent with what is known about related processes.[1] Presumably, not only the reactions of α-nitrocumene, *p*-cyano-α-nitrocumene, and the fluorinated α-nitrocumene **7**, but also the reactions of the other α-arylated tertiary nitro compounds proceed via a radical anion–free radical chain sequence such as that shown in eq 6–9 for α-nitrocumene.

Finally, it should be pointed out that very small amounts of two byproducts are often produced in these reactions. One is the dimer of the cumyl radical (**9**), the other the reduction product of the β-arylated nitroparaffin (**10**).


9


10

In this connection the reaction of α-nitrocumene (**2**) with the lithium salt of 2-nitropropane is of interest. This reaction is very slow; after 6 days NMR analysis indicates that 22% of the α-nitrocumene is still unreacted, that the β-phenylated nitroethane (2,3-dimethyl-2-phenyl-3-nitrobutane) is formed in 30% yield, and that the bicumyl is produced in 48% yield. While these data are not definitive there can be little doubt that in this one case the desired reaction is not the major process.[21] That this is so appears to derive from a combination of steric and electrical effects. In the first place, as shown in eq 2, α-nitrocumene when treated with the lithium salt of nitroethane readily gives the β-arylated nitroparaffin and not the cumyl dimer. This suggests that the enhanced steric requirement in going from the anion of nitroethane to that of 2-nitropropane is a significant adverse influence. But, as can be seen from eq 5 and Table I, α-nitrocumenes bearing electron-withdrawing substituents react readily with the lithium salts of 2-nitropropane and 2-nitrobutane. Clearly, in these cases the steric factor is outweighed by a polar factor. One can only speculate as to how the polar factor operates; one possibility is that cumyl radicals bearing electron-withdrawing substituents possess heightened electrophilicity, so that the drive for reacting with a nitroparaffin anion to give a radical anion is greater than for the unsubstituted cumyl radical.

Experimental Section[8]

CAUTION: HMPA should be handled with great care since it has recently been found to cause cancer in laboratory animals [*Chem. Eng. News*, 54 (39), 17 (1975)].

α-Arylated Nitro Compounds. Most of the α-arylated nitro compounds employed in this study are known and their synthesis from substituted nitrobenzenes has been described.[4] The following preparations are new.

2-(*p*-Cyanophenyl)-2-nitrobutane. The lithium salt of 2-nitrobutane (10.9 g, 100 mmol),[9] *p*-cyanonitrobenzene (7.40 g, 50 mmol), 100 mL of HMPA, and a reaction time of 17 h were employed.[4] On workup 9.6 g of an orange oil was obtained. This was chromatographed through a short column of alumina using benzene as the eluent. The resulting 8.90 g of product, when Kugelrohr distilled at 1 mm and 120 °C, gave 8.81 g of a light yellow oil (87% yield): NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.96 (s, 3 H), 2.18–2.55 (m, 2 H), 7.35–7.85 (m, 4 H); IR (neat) 4.45 (CN), 6.49, 7.40 (NO_2) μm.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.69; H, 5.66; N, 13.54.

2-*m,m'*-Bis(trifluoromethyl)phenyl-2-nitrobutane. 3,5-Bis(trifluoromethyl)nitrobenzene (10.35 g, 39.77 mmol) and the lithium salt of 2-nitrobutane (4.70 g, 43.1 mmol) were allowed to react in 50 mL of HMPA under argon. Workup after 24 h and crystallization from hexane gave colorless crystals: mp 43–44 °C; NMR ($CDCl_3$) δ 0.97 (t, 3 H), 2.01 (s, 3 H), 2.48 (m, 2 H), 7.89 (br s, 3 H); IR ($CHCl_3$) 6.47, 6.85, 7.25 μm.

Anal. Calcd for $C_{12}H_{11}NO_2F_6$: C, 45.57; H, 3.83; N, 4.43; F, 36.06. Found: C, 45.35; H, 3.75; N, 4.23; F, 35.81.

α-Nitrocumene (**2**) was obtained from α-methylstyrene via the following intermediates.

***N*-α-Cumylformamide.** α-Methylstyrene (236 g) was subjected to the Ritter reaction;[10] 120 g (36% yield) of slightly impure *N*-α-cumylformamide was obtained. For analysis a small portion of the formamide was passed through silica gel using chloroform as the eluent; the first fraction was largely composed of an impurity. Continued elution with chloroform and then with ethyl acetate gave a yellow oil which after Kugelrohr distillation at 0.1 mm and 93 °C is colorless: n^{23}_D 1.5371; NMR ($CDCl_3$) δ 1.53 (s, 3 H), 1.57 (s, 3 H), 7.0–8.2 (m, 7 H); IR (neat) 3.06 (NH), 3.65 (O=CH), 6.0 (C=O) μm.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.44; H, 7.82; N, 8.40.

α-Aminocumene. This was obtained on alkaline hydrolysis of the formamide;[10] from 111.7 g of the slightly impure formamide, 61.9 g (67% yield) of pure α-aminocumene was isolated: bp 94 °C (26 mm); n^{24}_D 1.5174 (lit.[11] n^{25}_D 1.5175–1.5185); NMR ($CDCl_3$) δ 1.41 (s, 8 H), 7.1–7.2 (m, 5 H); IR (neat) 2.98, 3.07 (NH_2) μm.

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.03; H, 9.74; N, 10.55.

α-Nitrocumene (2). Permanganate oxidation[12] of 59.9 g of α-aminocumene gave 34.6 g (47% yield) of pure α-nitrocumene: bp 97 °C (5 mm); n^{25}_D 1.5178 (lit.[5] n^{20}_D 1.5204); NMR ($CDCl_3$) δ 1.95 (s, 6 H), 7.39 (s, 5 H); IR (neat) 6.55, 7.44 (NO_2) μm.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.60; H, 6.72; N, 8.50.

β-Arylated Nitroparaffins. General Procedure. The synthesis of compound 8 (the reaction of eq 5) is illustrative. The center neck of a 200-ml three-neck flask is fitted with an adapter constructed of a male and a female ground-glass joint separated by a stopcock. Each of the other two necks is fitted with an addition tube (A). These addition tubes are so constructed that their contents may be emptied into the flask without opening the system, merely by rotating around the joint (cf. Figure 1). One of the addition tubes is charged with 2.989 g (10 mmol) of 3,5-bis(trifluoromethyl)-α-nitrocumene (7)[4] and the other contains 4.75 g (50 mmol) of the lithium salt of 2-nitropropane;[13,9] a magnetic stirring bar and 100 mL of HMPA are placed in the flask.

The system is purged of air by evacuating and then bleeding in argon. This process is repeated three times and then the HMPA is frozen by liquid nitrogen. The system is evacuated to ~1 mm and the frozen HMPA is allowed to thaw. This freeze–pump–thaw procedure is repeated two more times and then argon at 1-atm pressure is bled in. [This rigorous degassing is probably not necessary in most cases. An alternative is to purge the system of air simply by evacuating and then bleeding in nitrogen; this procedure is repeated three times. A number of the reactions of Table I were run both "freeze–pump–thaw" and "under nitrogen" with identical results.]

The flask is placed under the light apparatus,[14] magnetic stirring is instituted, and the 2-nitropropane salt is added. After the salt has dissolved the 3,5-bis(trifluoromethyl)-α-nitrocumene (7) is added and the resulting solution is stirred for 16 h at room temperature. The solution is then poured into water and extracted with benzene. The benzene phase is washed with water and dried over anhydrous $MgSO_4$, and then the solvent is removed using a rotatory evaporator under reduced pressure. The resulting yellow oil (3.38 g) is dissolved in 15 mL of hexane and chromatographed on alumina. Elution with hexane quickly gives 0.08 g (2% yield) of a colorless liquid which has an NMR spectrum identical with that of authentic 2,3-dimethyl-2-[*m,m'*-bis(trifluoromethyl)phenyl]butane;[15] that is immediately followed by 0.06 g (1% yield) of the *m,m'*-bis(trifluoromethyl)cumyl dimer: mp 66.5–68 °C (lit.[16] mp 67–68 °C). Further elution with 90% hexane–10% benzene gives 3.06 g (90% yield) of the β-arylated nitroparaffin 8: colorless crystals; mp 49–50 °C; NMR (CCl_4) δ 1.50 (s, 6 H), 1.57 (s, 6 H), 7.77 (br s, 3 H).

Anal. Calcd for $C_{14}H_{15}F_6NO_2$: C, 48.99; H, 4.40; F, 33.21; N, 4.08; mol wt, 343. Found: C, 49.02; H, 4.41; F, 33.04; N, 4.08; mol wt, 344.

The reaction between 3,5-bis(trifluoromethyl)-α-nitrocumene (7) and the lithium salt of 2-nitropropane was also studied as regards the matter of mechanism. A duplicate of the foregoing experiment was carried out except that now 0.168 g (1 mmol) of *m*-dinitrobenzene was present. From the crude red-brown product (3.247 g) a total of 2.975 g (98% recovery) of pure 3,5-bis(trifluoromethyl)-α-nitrocumene (7) was obtained by recrystallization from hexane and chromatography on alumina: mp 54–55 °C. The NMR spectrum of this recovered material was identical with that of the starting material and it was pure by VPC. Thus, complete inhibition had occurred.

Another duplicate of the first experiment was carried out except that here di-*tert*-butyl nitroxide was present (0.110 g, 0.8 mmol). On workup and purification by chromatographing on alumina 2.558 g (85%) of the pure starting 3,5-bis(trifluoromethyl)-α-nitrocumene (7) was obtained: mp 54–55 °C. Its NMR spectrum was identical with that of the starting material and it was pure by VPC. Clearly, inhibition had occurred.

Finally, the first experiment was repeated exactly as described above except that now it was conducted in a dark room and the reaction flask was wrapped with aluminum foil. The crude product was a pale tan viscous oil (3.185 g). VPC analysis showed that 69% of this oil was unreacted α-nitrocumene 7 and 31% was the β-arylated nitroparaffin 8. The crude product was passed through a column of alumina and the resulting mixture was analyzed by VPC and by NMR. In this way it was found that 1.595 g of the resulting mixture was unchanged starting material (63% recovery) and that 0.963 g (28% yield) of the β-arylated nitroparaffin 8 was present. Thus this reaction will take place in the dark but at a distinctly slower rate than when exposed to two 20-W ordinary fluorescent lights.

2-Methyl-2-phenyl-3-nitrobutane. (A) Preparation. The reaction was carried out in a 25-mL three-neck flask according to the general procedure. Into one of the addition tubes (A) was placed 0.165 g (1 mmol) of α-nitrocumene and into the other addition tube was placed 0.162 g (2 mmol) of the lithium salt of nitroethane;[17] 10 mL of HMPA was placed in the flask. The HMPA was subjected to the freeze–pump–thaw procedure while the α-nitrocumene was kept frozen with dry ice. The contents of the two addition tubes were then transferred to the HMPA and the resulting mixture was stirred for 45 h under the light apparatus.[14] The yellow solution was then placed

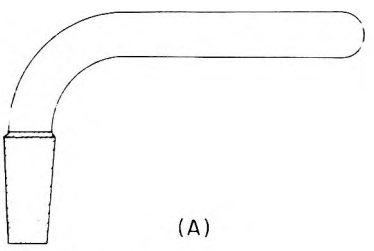


Figure 1. Addition tube (A).

in an ice bath and an ice-cold solution of urea (0.369 g) in 1.8 mL of 20% acetic acid–80% water[18] was added all at once. The resulting solution was stirred for 10 min in the ice bath and then was poured into 200 mL of water containing ~2 g of NaCl. The cloudy aqueous HMPA solution was extracted repeatedly with pentane and the pentane extracts were then washed repeatedly with water. After drying over anhydrous $MgSO_4$ the pentane was removed on a rotary evaporator under reduced pressure. This gave 0.178 g of a colorless liquid which was separated into two fractions by preparative TLC (silica gel; 10% ethyl acetate–90% hexane). The first fraction (0.018 g) melted at 103–110 °C. On recrystallization from methanol 0.011 g (0.046 mmol; 9% yield) of 2,3-dimethyl-2,3-diphehylbutane was obtained: white needles; mp 116–117 °C (lit.[19] mp 118–119 °C); NMR ($CDCl_3$) δ 1.28 (s, 12 H), 7.15 (m, 10 H).

Anal. Calcd for $C_{18}H_{22}$: C, 90.70; H, 9.30; mol wt, 238. Found: C, 90.65; H, 9.30; mol wt, 238.

The second fraction (0.152 g) was Kugelrohr distilled at 57 °C (0.01 mm), whereupon 0.143 g of a colorless liquid, n^{22}_D 1.5200, was obtained; this is 2-methyl-2-phenyl-3-nitrobutane (74% yield). By TLC and VPC analysis this is a pure compound: NMR ($CDCl_3$) δ 1.29 (d, J = 7 Hz, 3 H), 1.44 (s, 6 H), 4.86 (q, J = 7 Hz, 1 H), 7.34 (m, 5 H); IR (neat) 6.52, 7.47 (NO_2) μm.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.01. Found: C, 68.14; H, 7.59; N, 7.25.

(B) The Effect of *m*-Dinitrobenzene. This experiment was a duplicate of the preceding one except that now a 25-mL four-neck flask containing three addition tubes (A) was used. The third addition tube contained 0.034 g (0.20 mmol) of *m*-dinitrobenzene and after the freeze–pump–thaw procedure this was added to the reaction mixture. Workup gave 0.178 g of a red liquid which on preparative TLC yielded 0.142 g of a pale yellow liquid. Kugelrohr distillation at 57 °C (0.1 mm) gave 0.135 g of a colorless liquid which NMR analysis reveals is a mixture of α-nitrocumene and 2-methyl-2-phenyl-3-nitrobutane in a ratio of 95:5. Thus, the 0.135 g of distillate corresponds to a 77% recovery of α-nitrocumene and a 4% yield of 2-methyl-2-phenyl-3-nitrobutane. The IR of this mixture is virtually identical with that of pure α-nitrocumene.

(C) The Effect of Di-*tert*-butyl Nitroxide. The first experiment of this group (A) was duplicated except that now a 50-mL four-neck flask containing three addition tubes was employed. The third addition tube contained 0.013 g (0.09 mmol) of di-*tert*-butyl nitroxide; during the freeze–pump–thaw deoxygenation procedure the nitroxide was kept frozen in dry ice to prevent loss by evaporation. Workup gave 0.169 g of a brown liquid from which, by preparative TLC, 0.133 g of a colorless liquid was obtained. Kugelrohr distillation at 57 °C (0.1 mm) gave 0.120 g (73% recovery) of α-nitrocumene. Its NMR, IR, and n^{25}_D are identical with that of the starting material. TLC and VPC analyses also attest to the purity of this recovered α-nitrocumene.

(D) The Effect of Light. Experiment A of this group was repeated except that it was conducted in a dark room and the system was completely wrapped in aluminum foil. Workup, followed by the usual preparative TLC and Kugelrohr distillation, gave 0.137 g (83% recovery) of a colorless liquid which by NMR analysis consisted of α-nitrocumene contaminated by a trace (<2%) of 2-methyl-2-phenyl-3-nitrobutane. The IR spectrum and the n^{25}_D of this material were identical with that of pure α-nitrocumene and the VPC and TLC analyses failed to reveal the presence of any impurity. Clearly, then, little if any reaction takes place in the dark in 45 h.

2-Methyl-2-*p*-cyanophenyl-3-nitrobutane (5). (A) Preparation. The reaction of *p*-cyano-α-nitrocumene[4] (0.190 g, 1 mmol) with 0.162 g (2 mmol) of the lithium salt of nitroethane[17] was carried out in 10 mL of HMPA according to the general procedure; a nitrogen purge was employed rather than the argon freeze–pump–thaw procedure. After 8 h the reaction flask was placed in an ice bath and a cold solution of 0.369 g (6 mmol) of urea dissolved in 1.8 mL of 20% acetic acid–80% water was added all at once. The solution was stirred for 10

min in an ice bath, after which it was poured into 200 mL of water containing ~2 g of NaCl. The aqueous HMPA solution was repeatedly extracted first with ethyl ether and then with benzene. The combined ether–benzene extracts were thoroughly washed with water and dried and then solvent was removed under reduced pressure. The 0.246 g of yellow liquid thus obtained was Kugelrohr distilled twice at 122 °C (0.1 mm). In this way 0.205 g (94% yield) of pure 2-methyl-2-(*p*-cyanophenyl)-3-nitrobutane (**5**) was obtained: mp 57–58 °C; NMR ($CDCl_3$) δ [1.4 (d, J = 7 Hz), 1.49 (s) 9 H], 4.82 (q, J = 7 Hz, 1 H), 7.4–7.8 (q, 4 H); IR (melt) 4.48 (C≡N), 6.48 (NO_2) μm.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.83; H, 6.26; N, 12.64.

On standing for 3 weeks the melting point of 2-methyl-2-(*p*-cyanophenyl)-3-nitrobutane changed to 62–65 °C; the IR and NMR spectra of the higher melting material were, however, identical with those of the lower melting form. After 8 months the melting points had become 65–66 °C and an elemental analysis gave the following results: C, 66.28; H, 6.69; N, 12.98. Clearly, the higher melting material is a second crystalline form of 2-methyl-2-(*p*-cyanophenyl)-3-nitrobutane.

(B) The Effect of *m*-Dinitrobenzene. This experiment was a duplicate of the preceding one except that now an additional side-arm addition tube (A) was employed; it contained 0.034 g (0.2 mmol) of *m*-dinitrobenzene. After adding the lithium salt of nitroethane to the HMPA the *m*-dinitrobenzene was introduced and, finally, the *p*-cyano-α-nitrocumene. On workup 0.229 g of an orange solid, mp 46–55 °C, was obtained; this, on Kugelrohr distillation at 90 °C (0.1 mm), gave 0.172 of a yellow solid: mp 55–59 °C. Recrystallization from hexane produced 0.136 g (77% recovery) of white needles: mp 61–62 °C. That this is the pure starting material (*p*-cyano-α-nitrocumene) was further shown by a mixed melting point and by VPC and TLC. Finally, the recovered material and the starting material have identical NMR and IR spectra.

(C) The Effect of Di-*tert*-Butyl Nitroxide. The first experiment of this group (A) was repeated except that 0.014 g (0.1 mmol) of di-*tert*-butyl nitroxide (which was kept frozen during the nitrogen purge) was introduced prior to the addition of the *p*-cyano-α-nitrocumene to the HMPA. Workup gave 0.188 g of crude product: mp 57–58 °C. This after two Kugelrohr distillations at 90 °C (0.1 mm) was white and had: mp 60–61 °C; 0.172 g (91% recovery). Pure *p*-cyano-α-nitrocumene melts at 61–62 °C; the melting point of a mixture was 60.5–61.5 °C. The recovered material was identical by NMR, IR, VPC, and TLC with the pure starting material.

(D) The Effect of Light. Experiment A of this group was duplicated except that it was carried out in a dark room and the reaction system was wrapped in aluminum foil. The crude product (0.184 g) melted at 59–61 °C. Kugelrohr distillation at 90 °C (0.1 mm) gave 0.168 g (88% recovery) of white needles, mp 61–62 °C. The melting point of a mixture of this material and pure *p*-cyano-α-nitrocumene was 61–62 °C. The recovered material was identical by NMR, IR, VPC, and TLC with the starting material.

(E) Analytical Sensitivity. Mixtures of the starting compound (**4**) and the product (**5**) of these reactions (cf. eq 4) were analyzed by NMR in $CDCl_3$. In this way it was shown that at the 3% level 2-methyl-2-*p*-cyanophenyl-3-nitrobutane (**5**) can unequivocally be detected. Since NMR analyses of the crude reaction products of experiments B, C, and D of this group gave no evidence of the presence of **5** it can safely be concluded that in those experiments <3% was produced.

2,3-Dimethyl-2-(*p*-cyanophenyl)-3-nitrobutane. (A) Preparation. *p*-Cyano-α-nitrocumene[4] (9.50 g, 50 mmol), the lithium salt of 2-nitropropane[9,13] (23.75 g, 250 mmol), 500 mL of HMPA, a nitrogen atmosphere, and a reaction time of 50 h were employed. The crude reaction product (10.3 g) was a yellow solid, the NMR analysis of which indicated that it was contaminated with *p*-cyanocumyl dimer. On recrystallizations from methanol 8.01 g (68% yield) of 2,3-dimethyl-2-(*p*-cyanophenyl)-3-nitrobutane was obtained: mp 166–167 °C; NMR ($CDCl_3$) δ 1.53 (s, 12 H), 7.25–7.75 (m, 4 H).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.14; H, 6.89; N, 11.93.

(B) Mechanistic Studies. The reaction of *p*-cyano-α-nitrocumene (**4**) with the lithium salt of 2-nitropropane was studied under argon using the freeze–pump–thaw technique (vide supra) to remove oxygen from the system. Each experiment of this set employed 0.190 g (1 mmol) of *p*-cyano-α-nitrocumene, 0.480 g (5 mmol) of the lithium salt of 2-nitropropane, 10 mL of HMPA, magnetic stirring, and a 36-h reaction time. Except for the dark experiment (see below) the reactions were conducted under the light apparatus.[14] The reaction mixture was poured into water containing sodium chloride and extracted with ether and benzene. The combined extracts were washed with water and dried and the solvents were removed under reduced pressure, thereby giving the crude product.

In the absence of inhibitors the crude product was a pale yellow solid (0.211 g): mp 133–155 °C. Kugelrohr distillation at 60 °C (0.1 mm) gave 0.012 g of a colorless, multicomponent liquid which was not further investigated. On raising the temperature to 100 °C a pale yellow solid (0.176 g) sublimed; on recrystallization from methanol 0.123 g of white plates were obtained: mp 167–168 °C. This is a 53% yield of pure 2,3-dimethyl-2-(*p*-cyanophenyl)-3-nitrobutane (**6**). On raising the temperature of the Kugelrohr oven to 131 °C (0.1 mm) a tan solid (0.019 g) sublimed over; two recrystallizations of this material from methanol yielded 0.010 g of a tan solid: mp 218–219 °C. The melting point of authentic 2,3-dimethyl-2,3-di(*p*-cyanophenyl)butane (the *p*-cyanocumyl dimer) is 218.5–220 °C.[20] From the NMR spectrum in $CDCl_3$[20] it appears that the 0.010 g of tan solid is a mixture of the *p*-cyanocumyl dimer and 2,3-dimethyl-2-(*p*-cyanophenyl)-3-nitrobutane (**6**) in the ratio 88:12. The presence of the *p*-cyanocumyl dimer was established by exact mass spectroscopy. Calcd exact mass, 288.163; found, 288.164.

A duplicate experiment in which 0.032 g (0.20 mmol) of *m*-dinitrobenzene was present gave 0.208 g of a red liquid as the crude product. Preparative TLC, followed by recrystallization from hexane, yielded 0.143 g (75% recovery) of pure *p*-cyano-α-nitrocumene (**4**): white needles; mp 61–62 °C. A mixed melting point was undepressed and the NMR and IR spectra were identical with those of the starting material.

A duplicate of the first experiment except that now 0.029 g (0.20 mmol) of di-*tert*-butyl nitroxide was present gave on workup 0.188 g of white crystals: mp 55–61 °C. By preparative TLC and recrystallization from hexane a total of 0.144 g (76%) of the starting *p*-cyano-α-nitrocumene (**4**) was recovered: mp 61–62 °C.

The final experiment of this group was a duplicate of the first except that it was conducted with complete exclusion of light. The crude product was a white solid: mp 58–62 °C. Kugelrohr distillation at 85 °C (0.1 mm), followed by preparative TLC and recrystallization from hexane gave 0.161 g (85% recovery) of pure *p*-cyano-α-nitrocumene: mp 61–62 °C.

2,3-Dimethyl-2-(*p*-cyanophenyl)-3-nitropentane. *p*-Cyano-α-nitrocumene[4] (1.90 g, 10 mmol), the lithium salt of 2-nitrobutane (5.45 g, 50 mmol), 100 mL of HMPA, the freeze–pump–thaw procedure, and a reaction time of 46 h were employed. The crude product was orange (2.72 g) and melted at 96–101 °C. It was Kugelrohr distilled at 100 °C (0.003 mm), whereupon 1.91 g of material, mp 103–106 °C, was obtained. This, on recrystallization from hexane gave 1.67 g (68% yield) of colorless crystals: mp 107–108 °C; NMR ($CDCl_3$) δ 0.82 (t, 3 H), 1.42 (s, 3 H), 1.51 (s, 6 H), 1.52 (m, 1 H), 2.37 (m, 1 H), 7.25–7.75 (m, 4 H).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.33; H, 7.60; N, 11.17.

2,3-Dimethyl-2-(*p*-benzenesulfonylphenyl)-3-nitrobutane. 4-Phenylsulfonyl-α-nitrocumene[4] (7.90 g, 26 mmol), the lithium salt of 2-nitropropane (26 g, 270 mmol), 250 mL of HMPA, under N_2, and a reaction time of 110 h were employed. Workup gave 10.1 g of an off-white solid, mp 135–139 °C, which after two recrystallizations from methanol melts at 143–143.5 °C (6.33 g; 71% yield): NMR ($CDCl_3$) δ 1.48 (s, 12 H), 7.33–7.63 (m, 5 H), 7.70–8.05 (m, 4 H).

Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.25; H, 6.05; N, 4.03; S, 9.22; mol wt, 347. Found: C, 61.98; H, 5.87; N, 3.86; S, 9.04; mol wt, 343.

2,3-Dimethyl-2-*m,m'*-bis(trifluoromethyl)phenyl-3-nitropentane. *m,m'*-Bis(trifluoromethyl)-α-nitrocumene[4] (3.40 g, 11.3 mmol), the lithium salt of 2-nitrobutane (6.15 g, 56.5 mmol), 80 mL of HMPA, the freeze–pump–thaw procedure, and a reaction time of 45 h were employed. The crude product was chromatographed on acid-washed alumina using cyclohexane and then benzene as eluents. Recrystallization from cyclohexane gave 2.0 g of colorless crystals (50% yield): mp 94–96 °C; NMR ($CDCl_3$) δ 0.83 (t, 3 H), 1.47 (s, 3 H), 1.58 (s, 6 H), 1.70 (m, 1 H), 2.36 (m, 1 H), 7.84 (s, 3 H); IR ($CHCl_3$) 6.54, 7.32, 7.85 μm.

For analysis a sample was sublimed: mp 94.5–96 °C.

Anal. Calcd for $C_{15}H_{17}NO_2F_6$: C, 50.42; H, 4.79; N, 3.92; F, 31.90. Found: C, 50.43; H, 4.77; N, 3.90; F, 31.95.

2,3-Dimethyl-2-(*p*-benzoylphenyl)-3-nitrobutane. 4-Benzoyl-α-nitrocumene[4] (2.69 g, 10 mmol), the lithium salt of 2-nitropropane (4.75 g, 50 mmol), 100 mL of HMPA, the freeze–pump–thaw procedure, and a reaction time of 72 h were employed. On workup 2.807 g of an orange solid, mp 95–100 °C, which NMR spectroscopy indicated was contaminated with *p*-benzoylphenylcumyl dimer, was obtained. Kugelrohr distillation at 120 °C (0.006 mm) gave 2.431 g of material: mp 102–104 °C. The pure product was obtained on recrystallization from a chloroform–hexane mixture: 1.915 g (62% yield)

of colorless crystals; mp 109–110 °C; NMR ($CDCl_3$) δ 1.53 (s, 12 H), 7.3–7.9 (m, 9 H).

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.35; H, 6.60; N, 4.48.

2,3-Dimethyl-2-(*p*-benzoylphenyl)-3-nitropentane. 4-Benzoyl-α-nitrocumene[4] (2.69 g, 10 mmol), the lithium salt of 2-nitrobutane[9,15] (5.45 g, 50 mm), 100 mL of HMPA, the freeze–pump–thaw procedure, and a reaction time of 74 h were employed. Workup yielded 3.31 g of an oil which, when Kugelrohr distilled at 120 °C (0.004 mm) gave 2.60 g of a pale yellow oil. Crystallization from hexane produced 1.92 g (61% yield) of colorless crystals: mp 93.5–94.5 °C; NMR ($CDCl_3$) δ 0.82 (t, 3 H), 1.43 (s, 3 H), 1.54 (s, 6 H), 1.60 (m, 1 H), 2.41 (m, 1 H), 7.3–7.9 (m, 9 H).

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; Found: C, 74.04; H, 7.10; N, 4.56.

2,3-Dimethyl-2-(*p*-nitrophenyl)-3-nitropentane. α,*p*-Dinitrocumene[4] (7.00 g, 35 mmol), the lithium salt of 2-nitrobutane[9,13] (19.07 g, 175 mmol), 350 mL of HMPA, a nitrogen atmosphere, and a 6-h reaction time were employed. The crude product (8.6 g; mp 99–105 °C) was recrystallized from a hexane–chloroform mixture. This gave 6.93 g (74% yield) of pure product: mp 105.5–106 °C; NMR ($CDCl_3$) δ 0.80 (t, 3 H), 1.42 (s, 3 H), 1.52 (s, 6 H), 1.56 (m, 1 H), 2.46 (m, 1 H), 7.52 (m, 4 H).

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.85; H, 7.04; N, 10.47.

2,3-Dimethyl-3-(*p*-cyanophenyl)-2-nitropentane. 2-(*p*-Cyanophenyl)-2-nitrobutane (2.04 g, 10 mmol), the lithium salt of 2-nitropropane[9,13] (4.75 g, 50 mmol), 100 mL of HMPA, the freeze–pump–thaw procedure, and a reaction time of 92 h were employed. On workup 2.548 g of an orange oil was obtained; by NMR analysis the desired product was contaminated with 3,4-dimethyl-3,4-di-(*p*-cyanophenyl)hexane. Kugelrohr distillation at 100 °C (0.004 mm) gave 1.977 g of a yellow oil which crystallizes from hexane: mp 71.5–72.5 °C; yield, 1.48 g (60%); NMR ($CDCl_3$) δ 0.69 (t, 3 H), 1.50 (s, 6 H), 1.56 (s, 3 H), 1.55–2.65 (m, 2 H), 7.25–7.80 (m, 4 H).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.47; H, 7.36; N, 11.14.

2,3-Dimethyl-3-*m,m'*-bis(trifluoromethyl)phenyl-2-nitropentane. 2-*m,m'*-Bis(trifluoromethyl)phenyl-2-nitrobutane (2.50 g, 7.95 mmol) and the lithium salt of 2-nitropropane[9,13] (3.77 g, 39.6 mmol) were allowed to react in 60 mL of HMPA. The freeze–pump–thaw procedure and a reaction time of 45 h were employed. The crude product was distilled in the Kugelrohr apparatus at 70–80 °C (1 mm); this gave 1.7 g of a colorless oil (60% yield): NMR ($CDCl_3$) δ 0.74 (t, 3 H), 1.55 (s, 9 H), 1.65–2.80 (m, 2 H), 7.78 (br s, 2 H), 7.86 (br s, 1 H); IR ($CHCl_3$) 6.52, 7.30, 7.82 μm.

Anal. Calcd for $C_{15}H_{17}NO_2F_6$: C, 50.42; H, 4.79; N, 3.92; F, 31.90. Found: C, 50.77; H, 5.00; N, 3.95; F, 31.85.

2,3-Dimethyl-3-(*p*-nitrophenyl)-2-nitropentane. 2-(*p*-Nitrophenyl)-2-nitrobutane[4] (9.85 g, 44 mmol), the lithium salt of 2-nitropropane (20.84 g, 220 mmol), 300 mL of HMPA, and a reaction time of 3 h were employed. The crude product was purified by chromatography on acid-washed alumina using benzene as the eluent. This was followed by recrystallization from hexane: yield 8.9 g (76%) of pale yellow crystals; mp 94–95.5 °C; NMR ($CDCl_3$) δ 0.72 (t, 3 H), 1.55 and 1.58 (s each, total 9 H), 1.72 (m, 1 H), 2.36 (m, 1 H), 7.50 and 8.19 (AA′BB′ system with J_{AB} = 9 Hz., total 4 H); IR ($CHCl_3$) 6.25, 6.58, 7.40 μm.

For analysis a small sample was again recrystallized from a cyclohexane–benzene mixture: mp 96–97 °C.

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.78; H, 6.71; N, 10.30.

Solvent Effects. The effects of solvents on the reaction of *p*-cyano-α-nitrocumene (**4**) and of 3,5-bis(trifluoromethyl)-α-nitrocumene (**7**) with the lithium salt of 2-nitropropane were examined in a preliminary way. In both instances the reaction is much faster in HMPA than in Me_2SO or DMF. It is slowest in DMF, but the rate difference between DMF and Me_2SO is not large. Thus, in one set of experiments involving **4** when the reaction is 77% complete in HMPA it has proceeded only 26% in Me_2SO and 14% in DMF. Furthermore, the production of *p*-cyanocumyl dimer is highest in Me_2SO, next highest in DMF, and much the smallest in HMPA. Similar results were obtained in reactions employing **7**; the rate of reaction is unambiguously greater in HMPA than in the other two solvents. And here, again, the formation of cumyl dimer is minimal in HMPA.

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Registry No.—3,5-Bis(trifluoromethyl)nitrobenzene, 328-75-6; *N*-α-cumylformamide, 42044-69-9; α-methylstyrene, 98-83-9; α-aminocumene, 585-32-0; *m,m'*-bis(trifluoromethyl)cumyl dimer, 65253-47-6; 2,3-dimethyl-2,3-diphenylbutane, 1889-67-4; 2-methyl-2-(*p*-cyanophenyl)-3-nitrobutane, 65253-36-3; *p*-cyanocumyl dimer, 65253-48-7; *p*-cyanonitrobenzene, 619-72-7.

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Nucleophilic Step of Ring-Opening Reactions of Cyclopropanes with Electrophiles. Electronic Substituent Effects on Stereoselectivity of Reactions of Some 1-Arylbicyclo[4.1.0]heptanes with Mercuric Salts

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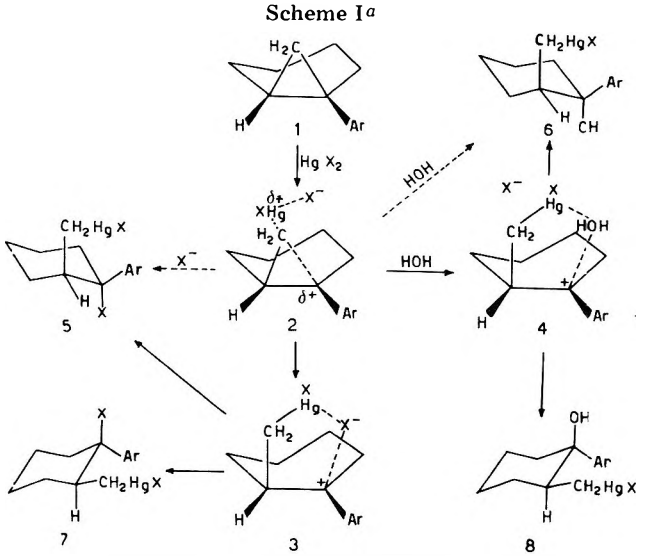
The stereochemistry of the nucleophilic step of the ring-opening reactions of 1-(*p*-tolyl)- (**1b**) and 1-(*m*-chlorophenyl)bicyclo[4.1.0]heptane (**1c**) with mercuric salts has been investigated and compared with that of the corresponding phenylcyclopropane (**1a**) in order to verify how a substituent on the phenyl of **1a**, modifying the conjugative ability of the aromatic system, could influence the stereochemical results. The mercuration reactions of **1b** and **1c** have a behavior parallel to that of **1a**: the stereoselectivity changes markedly with the salt and with the reaction conditions; however, all the percentages of syn products arising from the reactions of **1c** and most of those obtained in the ring opening of **1b** are slightly lower than the corresponding values obtained for the unsubstituted cyclopropane **1a**. Possible explanations of the observed stereochemical results have been given on the basis of a mechanism, modified from that previously suggested for **1a**, implying intermediate structures with a high degree of carbocationic character.

The ring opening of cyclopropanes by electrophiles occurs in the direction of the more stable carbocation with either retention or inversion of configuration at the site of the electrophilic attack, depending on the nature and configuration of the ring substituents, whereas the stereochemistry of the nucleophilic step takes place with complete or strongly predominant inversion of configuration.[1-4]

Recently it has been shown[5] that the ring opening of phenylcyclopropane **1a** with mercuric salts occurs, according to expectation,[1,2,4,6] by attack of the electrophile on the least-substituted carbon, in the direction of the benzylic carbon. However, the stereochemistry of the nucleophilic step was highly variable, ranging from almost complete inversion to markedly predominant retention of configuration depending on the type of mercuric salt and on the solvent.[5] The results obtained,[5] in agreement with kinetic results of the mercuration of arylcyclopropanes,[6] pointed to transition states or intermediates with a high degree of positive charge on the benzylic carbon. In order to justify the results a mechanism was suggested (see Scheme I)[5] analogous to the one previously postulated to rationalize the similar stereochemical behavior of the acid-catalyzed ring opening of 1-aryloxiranes.[7] Attack of the mercury (as HgX_2)[6] on the least-hindered carbon[1,2,4] of **1a** leads to a corner-mercurated intermediate which can evolve through an incipient carbenium ion (like **2**) to selectively interacting ion–nucleophile pairs (**3** for reaction in nonnucleophilic solvents and **4** for reactions in nucleophilic solvents). According to the mechanistic scheme proposed,[5] the anti adducts **5** or **6** should have arisen by attack of the nucleophile (X^- or SOH) at the stage of the incipient carbenium ion **2**, whereas collapse of the ion–nucleophile pairs should have afforded the syn compounds **7** or **8**. Evidently in such a mechanism every factor affecting the relative stability of structures **2**, **3**, or **4** and their reactivity should also modify the syn/anti ratio; factors favoring the development of the positive charge on the benzylic carbon should increase this ratio.

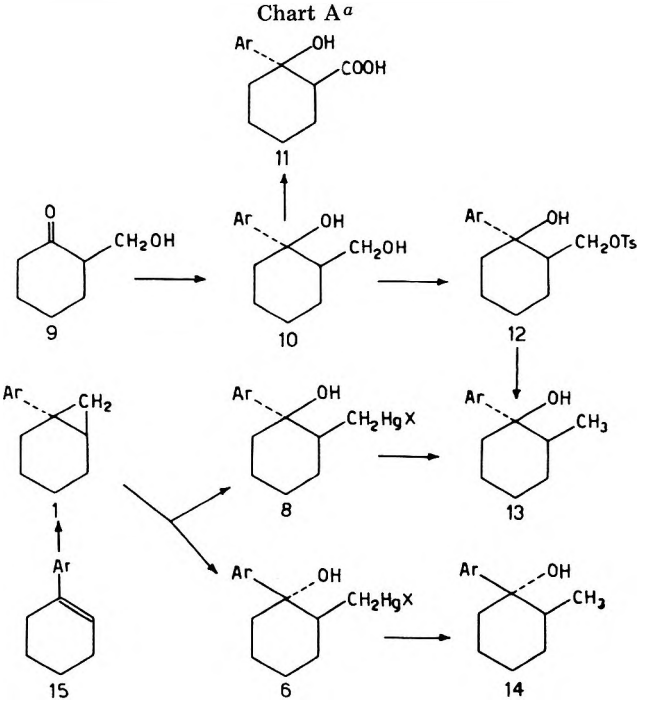
It was therefore of interest to study how a substituent on

Scheme I[a]



[a] a, Ar = C_6H_5; b, Ar = *p*-$CH_3C_6H_4$; c, Ar = *m*-ClC_6H_4.

Chart A[a]



[a] b, Ar = *p*-$CH_3C_6H_4$; c, Ar = *m*-ClC_6H_4; X = CH_3COO, CF_3COO, NO_3, ClO_4.

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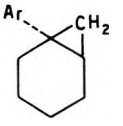
Table I. Stereochemistry of the Nucleophilic Step of the Mercuration of Cyclopropane 1

Cyclo-propane	Registry no.	Mercuric salt	Registry no.	Solvent	Cis (13)/trans (14) ratio
1a	2415-82-9	$Hg(OOCCH_3)_2$	1600-27-7	H_2O	13.5:86.5[a]
b	64705-88-0				11.2:88.8
c	64705-89-1				9.2:90.8
a		$Hg(OOCCF_3)_2$	13257-51-7	H_2O	19.5:80.5[a]
b					22.5:77.5
c					15.3:84.7
a		$Hg(NO_3)_2$	10045-94-0	H_2O	22.5:77.5[a]
b					21.4:78.6
c					16.3:83.7
a		$Hg(ClO_4)_2$	7616-83-3	H_2O	23.0:77.0[a]
b					22.3:77.7
c					18.8:81.2
a		$Hg(OOCCH_3)_2$		THF–H_2O (1:1)	25.5:74.5[a]
b					18.1:81.9
c					23.4:76.6
a		$Hg(OOCCF_3)_2$		THF–H_2O (1:1)	28.5:71.5[a]
b					22.9:77.1
c					28.3:71.7
a		$Hg(OOCCH_3)_2$		CH_2Cl_2	58.0:42.0[a]
b					59.1:40.9
c					52.3:47.7
a		$Hg(OOCCF_3)_2$		CH_2Cl_2	75.0:25.0[a]
b					67.3:32.7
c					74.0:26.0

[a] Reference 5.

the phenyl of **1a**, modifying the conjugative ability of the aromatic system, could influence the stereochemistry of the nucleophilic step of the cyclopropane ring opening with mercuric salts. The present investigation deals with the synthesis and the study of the mercuration reactions of cyclopropanes **1b** and **1c**. The *p*-methyl in **1b**, because of its electron-donating properties, should stabilize a benzylic electron-deficient center,[7c,8] whereas the overall electron-withdrawing effect of the *m*-chloro group in **1c** should have an opposite result.[7c,9]

Cyclopropanes **1b** and **1c** have been obtained by the Simmons–Smith reaction of the corresponding olefins **15b** and **15c** and have been purified by treatment with ozone followed by chromatography. Analogously to the unsubstituted cyclopropane **1a**,[5] the hydroxymercuration of **1b** and **1c** with mercuric acetate and mercuric trifluoroacetate in water yielded mixtures of the two corresponding organomercurials *cis*-**8** and *trans*-**6**, in which the latter predominated (see below) and was obtained in a pure state by crystallization. Reductive demercuriation of the trans organomercurials **6b** and **6c** (X = $OOCCH_3$ and $OOCCF_3$) gave the corresponding practically pure trans alcohols **14b** and **14c**. The diastereoisomeric cis alcohols **13b** and **13c** have been prepared in a pure form through unequivocal stereospecific syntheses. The reaction of 2-hydroxymethylcyclohexanone (**9**) with an excess of the suitable arylmagnesium bromide afforded mixtures consisting mainly of the cis diols **10b** and **10c**[10] accompanied by small amounts of their corresponding trans isomers, from which the former were obtained by crystallization. The diols **10b** and **10c** were transformed into their corresponding primary monotosylates **12b** and **12c**, which on reduction with $LiAlH_4$ afforded the alcohols **13b** and **13c** having the same relative configuration as the starting diols **12b** and **12c**. Pure alcohol **13b** has been also obtained by the reaction of 2-methylcyclohexanone with *p*-tolylmagnesium bromide, followed by column chromatography; in this reaction the trans isomer **14b** is practically absent (<2%). The configuration of the *p*-methyl-substituted cis diol **10b** has been proven, as has also that of the *m*-chloro analogue **10c**,[10] by its IR spectrum in the 3-μm range in a dilute solution of CCl_4, which showed



1

a, Ar = C_6H_5
b, Ar = p-CH_3 C_6H_4
c, Ar = m-Cl C_6H_4

Figure 1. Structure of cyclopropanes (1).

a strong band at 3507 cm^{-1}, indicative of a strong intramolecular OH···O bond[10,11] possible in both chair conformers of **10b**. Further confirmation of the configuration of **10b** has been given by the ^1H NMR spectrum of the acid **11b** obtained by Jones oxidation of **10b**. Keeping in mind that the aryl group, due to its larger steric hindrance, should occupy an equatorial position in the preferred conformation of **11b**, the relatively high half-band width (18 Hz)[10,12] of the signal of the proton α to the carboxy group allows one to infer the relative configuration of **11b** and consequently of **10b**. The structures of alcohols **13** and **14** have been confirmed on the basis of their ^1H NMR spectra.

The hydroxymercuration reactions of **1b** and **1c** have been carried out in H_2O and H_2O–THF with several salts, and the crude mixtures of the hydroxymercurials **8b, 6b** and **8c, 6c** have been analyzed, as was previously done for the mercuration reactions of **1a**,[5] through reductive demercuriation of the crude reaction mixtures with $NaBH_4$,[13] followed by GLC of the corresponding alcohols **13** and **14** (see Table I). Mercuration of **1b** and **1c** with $Hg(OOCCH_3)_2$ and $Hg(OOCCF_3)_2$ in CH_2Cl_2 yielded mixtures of the corresponding acyloxyorganomercurials *cis*-**7** and *trans*-**5** (X = $OOCCH_3$ or $OOCCF_3$),[5] whose ratios were determined by their reduction with $LiAlH_4$ to the alcohols **13b, 14b** and **13c, 14c**, respectively, followed by GLC analysis. The results of the nucleophilic step of the mercuration reactions of cyclopropanes **1b** and **1c** are summarized in Table I. Furthermore, the corresponding data for the unsubstituted cyclopropane **1a** have also been reported in the same table for the sake of comparison.

A first inspection of the results obtained (see Table I) shows that, as for the stereochemistry of the nucleophilic step, the mercuration reactions of cyclopropanes **1b** and **1c** have a behavior parallel to that of the phenylcyclopropane **1a** previously studied.[5] It can be observed that the stereoselectivity of the nucleophilic step of the mercuration of all the cyclopropanes **1a–c** changes markedly with the nature of the salt and with the reaction conditions. Higher percentages of syn adducts are formed when the reactions are carried out in the aprotic solvent (CH_2Cl_2), whereas the lower syn percentages are obtained in the reactions in H_2O when less ionic mercuric salt (mercuric acetate) is used. Furthermore, it may be pointed out that all the percentages of syn products arising from the reactions of *m*-chloro-substituted cyclopropane **1c** and most of those obtained in the ring opening of the *p*-methyl-substituted cyclopropane **1b** are slightly lower than the corresponding values obtained in the reactions of the unsubstituted cyclopropane **1a**,[5] even if the differences observed are relatively small.

In connection with the previously proposed mechanism[5] (see above), on the basis of the well-known electronic effects of the substituents (*p*-methyl and *m*-chloro)[9,10] and the known effect of such substituents on the stereochemistry of the acid-catalyzed ring opening of 1-aryloxiranes,[7c] it would be anticipated that in the case of cyclopropane **1c** the *m*-chloro substituent, which reduces the stability of the benzylic electron-deficient center, compared with the unsubstituted compound **1a**, should have favored (see Scheme I; no conformational implication is given to formulas) structures of type **2** more than those of type **3** or **4**, facilitating the formation of the anti adducts **5** and **6** in agreement with the experimental results. On the contrary, in the case of the cyclopropane **1b**, the *p*-methyl group should cause an opposite effect, thus favoring intermediates **3** and **4** and therefore the formation of the syn adducts **7** and **8** in contrast with the experimental results observed. Evidently the mechanism previously suggested in order to rationalize the results of the mercuration of **1a**[5] has to be modified. It must be pointed out, however, that the aryl group has to be important in determining the course of the mercuration of these compounds. As a matter of fact, apart from the clear directive effect of the aryl group in the regioselectivity of these reactions, the stereochemistry of the nucleophilic step of the mercuration of cyclopropanes carrying no aryl group on the ring is completely anti.[1,2,4] Furthermore, it must be kept in mind that the lack of complete anti stereoselectivity in the reactions under consideration clearly implies intermediate structures with high degrees of carbocationic character; the intervention of structures of this type in the mercuration of arylcyclopropanes was supported by a Hammett-type plot of the mercuration rates of arylcyclopropanes.[6] It could be that in the mercuration of cyclopropanes **1**, unlike the acid-catalyzed ring opening of oxiranes,[7] the attack of the nucleophile on the more carbocationic structures **3** and **4** is not completely syn stereoselective and therefore that the formation of both the syn as well as the anti products and consequently the different stereoselectivity of the reactions of each cyclopropane should be mainly due to differences in solvation of the intermediates and to differences in the stability of the selectively interacting ions **3** and **4**. For example, the increase of syn adduct in the mercuration of cyclopropanes **1** in aqueous solvent when the mercuric salt is changed from mercuric acetate to more highly ionic salts could be due to a strong interaction between mercury and the water molecule of **4**. Structures of type **2** in which the C–C bond is not completely broken should be no longer the solely responsible structures for determining the amount of anti adducts (**5** and **6**); perhaps in the present case structures of type **2** could rapidly evolve to the more carbocationic ones, **3** and **4**, before the attack of the nucleophile. However, the steps **2** → **5** or **2** → **6** cannot be completely ruled out. In conclusion, notwithstanding some analogies found between the stereoselectivity of the acid-catalyzed ring opening of aryloxiranes and the mercuration of arylcyclopropanes, the results obtained indicate sensible differences in the mechanisms responsible for the stereochemistry of these reactions.

Experimental Section

All melting points were taken on a Kofler micro hot stage and are uncorrected. Infrared spectra were measured with a Perkin-Elmer Infracord Model 137 on paraffin oil mulls, and the determination of OH stretching bands of **10b** was made with a Perkin-Elmer Model 257 double-beam grating spectrophotometer in dried (P_2O_5) CCl_4 using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2-cm optical length was employed, and the concentration of the solution was lower then 5×10^{-3} M to prevent intermolecular association. The NMR spectra were determined in ca. 10% $CDCl_3$ solutions with a Jeol C 60 HL spectrometer using tetramethylsilane as an internal standard. All GLC analyses were performed on a Carlo Erba Fractovap GV apparatus with a flame ionization detector using a dual column system with glass columns (1.5 mm × 2.5 m) packed with 10% Carbowax 20M on 80–100 mesh silanized Chromosorb W: column, 160 °C; evaporator, 200 °C; detector, 200 °C; nitrogen flow, 30 mL/min. The order of increasing retention times was **13b**, **14b**, **13c**, and **14c**. The relative percentages of compounds **13** and **14** were obtained from two or more separate runs on each experiment. Preparative TLC was performed on 2-mm silica gel plates (Merck F_{254}) containing a fluorescent indicator; spots were detected under UV light (245 nm). All comparisons between compounds were made on the basis of IR and NMR spectra and GLC. $MgSO_4$ was always used as a drying agent. Evaporations were made in vacuo (rotating evaporator). Petroleum ether refers to the fraction boiling at 40–70 °C. CH_2Cl_2 was dried over P_2O_5.

1-(*p*-Tolyl)cyclohexene (15b),[14] 1-(*m*-chlorophenyl)cyclohexene (15c),[14] 2-hydroxymethylcyclohexanone (9),[15] and 1-(*m*-chlorophenyl)-*c*-2-tosyloxymethyl-*r*-1-cyclohexanol (12c)[10] were prepared as previously described.

1-(*p*-Tolyl)bicyclo[4.1.0]heptane (1b). A mixture of zinc dust (34.6 g, 0.53 g-atom) and cuprous chloride (5.24 g, 0.053 mol) in anhydrous ether (60 mL) was stirred rapidly and refluxed vigorously for 1 h.[16] After cooling, a few crystals of iodine and then 1-(*p*-tolyl)cyclohexene (**15b**, 20.0 g, 0.116 mol) were added to the zinc–copper couple. The well-stirred mixture was then treated dropwise with methylene iodide (94.8 g, 0.353 mol) to maintain spontaneous refluxing. When the addition was complete the mixture was stirred and refluxed for an additional 24 h. After cooling, the reaction mixture was treated with saturated aqueous NH_4Cl and the ether layer was separated. The aqueous mixture was extracted with ether, and then the organic extracts were washed with water, saturated aqueous $NaHCO_3$, and water, dried, and evaporated to yield crude **1b** (19.5 g), which was ozonized in $CHCl_3$ at 0 °C for 1 h in order to eliminate traces of olefinic products. The chloroformic solution was washed with 2 N Na_2CO_3 and water and evaporated to dryness, and the residue was chromatographed on a 3 × 70 cm column of Al_2O_3 (activity I) using petroleum ether as the eluent and collecting 50-mL fractions. The 5th and the 6th fractions yielded pure **1b** (GLC): 6.5 g; NMR δ 2.25 (s, 3, CH_3), 1.05–0.42 (m, 2, cyclopropane protons); the signal of the third cyclopropane proton is overlapped with the methylenic envelope. Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.73. Found: C, 90.16; H, 9.75.

1-(*m*-Chlorophenyl)bicyclo[4.1.0]heptane (1c). Reaction of 1-(*m*-chlorophenyl)cyclohexene (**15c**, 10.0 g, 0.052 mol) with a zinc–copper couple,[16] prepared from zinc dust (17.3 g, 0.26 g-atom) and cuprous chloride (2.61 g, 0.026 mol) in anhydrous ether (30 mL) with methylene iodide (47.4 g, 0.17 mol) as described above for the preparation of **1b**, yielded a crude mixture which was ozonized in $CHCl_3$ according to the procedure described for **1b**. Evaporation of the washed (saturated aqueous $NaHCO_3$ and water) $CHCl_3$ solution yielded crude **1c** (8.9 g), which was purified by chromatography on a 2 × 40 cm column of Al_2O_3 (activity I) using petroleum ether as the eluent and collecting 50-mL fractions. Fractions 2–10 yielded pure **1c** (GLC): 5.2 g; NMR δ 1.05–0.54 (m, 2, cyclopropane protons); the signal of the third cyclopropane proton is overlapped with the methylenic envelope. Anal. Calcd for $C_{13}H_{15}Cl$: C, 75.53; H, 7.31. Found: C, 75.45; H, 7.59.

1-(*p*-Tolyl)-*c*-2-hydroxymethyl-*r*-1-cyclohexanol (10b). A solution of **9** (10.0 g, 0.078 mol) in anhydrous ether (20 mL) was added dropwise to a Grignard reagent prepared from *p*-bromotoluene (29.7

g, 0.17 mol) and magnesium (4.15 g, 0.17 g-atom) in anhydrous ether (65 mL). When the addition was complete the reaction mixture was refluxed for 3 h and then hydrolyzed with crushed ice, saturated aqueous NH_4Cl, and then diluted aqueous HCl. The organic layer was separated, and the aqueous portion was extracted with ether. Evaporation of the washed (H_2O, 10% aqueous Na_2CO_3, and H_2O) and dried ether extracts yielded an oily product (11.0 g) from which pure **10b** (2.1 g) was obtained by crystallization from petroleum ether at −5 °C, mp 48–49 °C; IR (CCl_4) ν(OH) 3638 (s, free OH), 3500 cm^{-1} (s, OH···O); NMR δ 3.48 (m, 2, CH_2OH) 2.36 (s, 3, $C_6H_4CH_3$). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.14. Found: C, 76.21; H, 9.27.

2-(*p*-Tolyl)-*c*-2-hydroxy-*r*-1-cyclohexanecarboxylic Acid (11b). A solution of **10b** (0.185 g, 0.84 mmol) in acetone (20 mL) was treated dropwise with Jones reagent[17] (0.44 mL) and left 10 min at room temperature. The mixture was diluted with water and extracted with ether, and the ether portion was extracted with 10% aqueous Na_2CO_3. Acidification of the alkaline solution with 10% aqueous HCl, extraction with ether, and evaporation of the washed ether extracts yielded crude **11b** (0.130 g) as a solid, which was recrystallized from petroleum ether (bp 60–80 °C) to give pure **11b** (0.080 g), mp 163–164 °C; IR λ 5.97 μm; NMR δ 2.95 (m, 1, W = 18 Hz, CHCOOH), 2.30 (s, 3, $C_6H_4CH_3$). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.00; H, 7.77.

1-(*p*-Tolyl)-*c*-tosyloxymethyl-*r*-1-cyclohexanol (12b). Tosyl chloride (1.85 g, 9.70 mmol) was slowly added to a solution of **10b** (0.46 g, 2.08 mmol) in dry pyridine (6 mL) while keeping the temperature at about 5 °C. After 4 days at room temperature the reaction mixture was treated with crushed ice and extracted with $CHCl_3$. The organic extracts were washed with dilute H_2SO_4 and water and evaporated to give a crude product (0.56 g) which crystallized from CCl_4 to yield pure **12b** (0.41 g), mp 131–133 °C; IR λ (OH) 2.86 μm; NMR δ 3.82 (d, 2, J = 5.3 Hz, CH_2O), 2.47 (s, 3, $OSO_2C_6H_4CH_3$), 2.36 (s, 3, $C_6H_4CH_3$). Anal. Calcd for $C_{21}H_{26}O_4S$: C, 67.35; H, 6.99. Found: C, 67.23; H, 6.75.

1-(*p*-Tolyl)-*c*-2-methyl-*r*-1-cyclohexanol (13b). (A) A solution of 2-methylcyclohexanone (24.7 g, 0.22 mol) in anhydrous ether (50 mL) was added dropwise to the Grignard reagent prepared from *p*-bromotoluene (48.7 g, 0.28 mol) and magnesium (6.8 g, 0.28 g-atom) in anhydrous ether (75 mL). When the addition was complete the resulting mixture was refluxed for 2 h and then left for 12 h at room temperature. After cooling, the mixture was treated with crushed ice, saturated aqueous NH_4Cl, and diluted aqueous HCl. The organic layer was separated, and the aqueous portion was extracted with ether. The combined ether extracts were washed (H_2O, 10% aqueous Na_2CO_3, and H_2O), dried, and evaporated to yield an oily residue (38.7 g) which was distilled to give an oil (34.0 g), bp 154–157 °C (10 mm), consisting essentially of **13b**; the trans isomer **14b** was practically absent (<2%). The distilled oil (3.0 g) was purified by chromatography through a 2 × 50 cm column of silica gel prepared in petroleum ether. On eluting in succession with petroleum ether (4 L), 98:2 petroleum ether–ether (3 L), and 97:3 petroleum ether–ether (2 L), pure **13b** was obtained (1.1 g, eluted with 98:2 petroleum ether–ether) as an oil: IR λ (OH) 2.87 μm; NMR δ 2.32 (s, 3, $C_6H_4CH_3$), 0.62 (d, 3, J = 6.0 Hz, $CHCH_3$). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.86. Found: C, 82.17; H, 9.72.

(B) A solution of **12b** (0.35 g, 0.93 mmol) in anhydrous ether was added dropwise to a stirred suspension of $LiAlH_4$ (0.70 g, 18.4 mmol) in anhydrous ether (20 mL). When the addition was complete the reaction mixture was refluxed for 15 h, the excess hydride was decomposed with a minimum amount of water and 2 N NaOH, and the dried ether layer was evaporated to dryness to yield pure **13b** (GLC).

1-(*m*-Chlorophenyl)-*c*-2-methyl-*r*-1-cyclohexanol (13c). A solution of **12c** (0.80 g, 2.02 mmol) in anhydrous ether (30 mL) was added to a stirred suspension of $LiAlH_4$ (1.52 g, 40.0 mmol) in anhydrous ether (50 mL). When the addition was complete the reaction mixture was refluxed for 1 hr, the excess hydride was decomposed with a minimum amount of water and 2 N NaOH, and the organic layer was separated and dried. Evaporation of the organic phase yielded an oily residue (0.38 g) consisting of **13c**, which was purified by preparative TLC; a 95:5 mixture of petroleum ether and ether was used as the eluent, yielding pure **13c** (0.21 g) (GLC) as an oil: IR λ (OH) 2.90 μm; NMR δ 0.62 (d, 3, J = 6.0 Hz, CH_3). Anal. Calcd for $C_{13}H_{17}ClO$: C, 69.47; H, 7.62. Found: C, 69.78; H, 7.55.

1-(*p*-Tolyl)-*t*-2-acetoxymercurimethyl-*r*-1-cyclohexanol (6b, X = CH_3COO). A stirred suspension of **1b** (0.72 g, 3.86 mmol) in water (70 mL) was treated with mercuric acetate (1.27 g, 3.98 mmol) and then stirred at room temperature for 3 days. After this time the reaction mixture was extracted with CH_2Cl_2, and the washed (H_2O) extracts were evaporated to give an oily residue (1.20 g) which on crystallization from benzene yielded pure **6b** (X = CH_3COO) (0.97 g), mp 142.5–143 °C; IR λ (OH) 2.93, (CO) 6.30 μm; NMR δ 2.37 (s, 3, $C_6H_4CH_3$), 1.90 (s, 3, $OCOCH_3$). Anal. Calcd for $C_{16}H_{22}O_3Hg$: C, 41.51; H, 4.79. Found: C, 41.86; H, 4.93.

1-(*p*-Tolyl)-*t*-2-trifluoroacetoxymercurimethyl-*r*-1-cyclohexanol (6b, X = CF_3COO). Mercuric trifluoroacetate[18] (0.85 g, 1.99 mmol) was added to a stirred suspension of **1b** (0.36 g, 1.93 mmol) in water (30 mL). After stirring for 3 days at room temperature, the reaction mixture was extracted with CH_2Cl_2 and the washed (H_2O) organic extracts yielded on evaporation a crude product (0.80 g) from which pure **6b** (X = CF_3COO) (0.34 g) was obtained by crystallization from benzene–petroleum ether (bp 80–100 °C): mp 132–133 °C; IR λ (OH) 2.91, (CO) 5.95 μm; NMR δ 2.35 (s, 3, $C_6H_4CH_3$). Anal. Calcd for $C_{16}H_{19}O_3F_3Hg$: C, 37.17; H, 3.70. Found: C, 37.53; H, 3.69.

1-(*m*-Chlorophenyl)-*t*-2-acetoxymercurimethyl-*r*-1-cyclohexanol (6c, X = CH_3COO). Reaction of **1c** (0.50 g, 2.4 mmol) with mercuric acetate in water as described above for the analogous reaction of **1b** (in the present case the reaction time was 5 days) yielded an oily residue (0.81 g) which crystallized from benzene, affording pure **6c** (X = CH_3CCO) (0.22 g), mp 132–133 °C; IR λ (OH) 2.95, (CO) 6.35 μm; NMR δ 1.95 (s, 3, CH_3). Anal. Calcd for $C_{15}H_{19}O_3ClHg$: C, 37.27; H, 3.96. Found: C, 37.60; H, 4.00.

1-(*m*-Chlorophenyl)-*t*-2-trifluoroacetoxymercurimethyl-*r*-1-cyclohexanol (6c, X = CF_3COO). Treatment of **1c** (0.50 g, 2.41 mmol) with mercuric trifluoroacetate[18] in water as described for the analogous reaction of **1b** (in the present case the reaction time was 5 days) yielded a crude product (0.95 g) which on crystallization from benzene–light petroleum (bp 60–80 °C) gave pure **6c** (X = CF_3COO)(0.43 g): mp 122–124 °C; IR λ (OH) 2.94, (CO) 5.97 μm. Anal. Calcd for $C_{15}H_{16}O_3ClF_3Hg$: C, 33.52; H, 3.00. Found: C, 34.07; H, 3.12.

1-(*p*-Tolyl)-*t*-2-methyl-*r*-1-cyclohexanol (14b). (A) A stirred suspension of **6b** (X = CH_3COO) (0.80 g, 1.72 mmol) in water (30 mL) was treated in succession with tetrahydrofuran (30 mL), 4 N NaOH (3.5 mL), and sodium borohydride (0.200 g, 5.28 mmol) and then stirred for 10 min. The reaction mixture was diluted with water and extracted with ether. Evaporation of the washed (H_2O) ether extracts yielded an oily residue (0.37 g) which was purified by preparative TLC (a 95:5 mixture of petroleum ether and ether was used as the eluent and elution was repeated twice). Pure **14b** was obtained (0.155 g) as a solid: mp 48–49 °C; IR λ (OH) 2.88 μm; NMR δ 2.36 (s, 3, $C_6H_4CH_3$), 0.65 (d, 3, J = 7.5 Hz, $CHCH_3$). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.86. Found: C, 82.20; H, 10.09.

(B) Compound **6b** (X = CH_3COO) (0.30 g, 0.65 mmol) was added to a stirred suspension of $LiAlH_4$ (0.150 g, 3.9 mmol) in anhydrous tetrahydrofuran and then the reaction mixture was stirred for 15 min. The excess hydride was decomposed with a minimum amount of water and 2 N NaOH, and the organic layer was separated. Evaporation of the dried organic phase yielded a residue (0.126 g) which consisted essentially of **14b**.

(C) Reduction of **6b** (X = CF_3COO) (0.25 g, 0.48 mmol) as described above in A for **6b** (X = CH_3COO) yielded a solid residue of **14b** (0.050 g).

1-(*m*-Chlorophenyl)-*t*-2-methyl-*r*-1-cyclohexanol (14c). (A) Reduction of **6c** (X = CH_3COO) (0.35 g, 0.72 mmol), as described above for the preparation of **14b** in A, gave crude **14c** (0.165 g), which was purified by preparative TLC (a 9:1 mixture of petroleum ether and ether was used as the eluent and elution was repeated twice), yielding pure **14c** (0.080 g) as an oil: IR λ (OH) 2.94 μm; NMR δ 0.66 (d, 3, J = 7.2 Hz CH_3). Anal. Calcd for $C_{13}H_{16}OCl$: C, 69.47; H, 7.62. Found: C, 69.82; H, 7.70.

(B) Compound **6c** (X = CF_3COO) (0.20 g, 0.37 mmol) was reduced as described above for the preparation of **14b** in A to yield crude oily **14c** (0.057 g).

Reaction of 1b and 1c with Several Mercuric Salts in Water. A suspension of the cyclopropane (**1b** or **1c**) (0.26 mmol) in water (5 mL) was treated with the appropriate mercuric salt (0.24 mmol) and then stirred at room temperature (3 h for the reactions of **1b** and 15 h for the reactions of **1c**). Then the reaction mixture was treated with tetrahydrofuran (4 mL), 4 N NaOH (0.5 mL), and sodium borohydride (0.027 g, 0.73 mmol), stirred for 10 min, diluted with water, and extracted with ether. Evaporation of the washed (water) and dried ether extracts yielded a residue which was analyzed by GLC. The ratios of **13** and **14** are shown in Table I. Reactions of **1b** and **1c**, carried out under the same conditions but reducing the mixtures after shorter reaction times (30 min and 1 h for **1b** and 5 h for **1c**), yielded the same product ratio within experimental error.

Reaction of 1b and 1c with Mercuric Acetate and Mercuric Trifluoroacetate in Tetrahydrofuran–Water. A solution of the cyclopropane (**1b** or **1c**) (0.26 mmol) in a 1:1 (v/v) tetrahydrofuran–

water mixture (5 mL) was treated with mercuric acetate or mercuric trifluoroacetate (0.24 mmol) and stirred at room temperature (3 and 6 h for the reaction of **1b** with mercuric acetate and mercuric trifluoroacetate, respectively, and 15 h for the reactions of **1c**). Then 4 N NaOH (0.5 mL) and sodium borohydride (0.027 g, 0.73 mmol) were added and stirring was continued for 10 min. The workup was carried out as described above for the reactions in water, and the residue obtained was analyzed by GLC. Reactions of **1** carried out under the same conditions but stopping after relatively longer contact times (24 h for both **1b** and **1c**) yielded the same product ratio within experimental error.

Reaction of 1b and 1c with Mercuric Acetate and Mercuric Trifluoroacetate in Anhydrous CH_2Cl_2. A solution of the cyclopropane (**1b** or **1c**) (0.26 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with the mercuric salt (0.24 mmol), stirred at room temperature (30 min for the reactions of **1b** and 24 h and 15 min for the reactions of **1c** with mercuric acetate and mercuric trifluoroacetate, respectively), then diluted with CH_2Cl_2, washed immediately with water, and evaporated. The residue (in the reactions with $Hg(OOCCF_3)_2$, λ (CO) 5.76, 6.20 μm for **1b** and 5.77 and 6.19 μm for **1c**; in the reactions with $Hg(OOCCH_3)_2$, λ (CO) 5.62, 5.95 μm for **1b** and 5.62 and 5.92 μm for **1c**) was taken up in anhydrous ether (10 mL), treated with $LiAlH_4$ (0.050 g, 1.31 mmol), stirred for 10 min at room temperature, and then refluxed for 10 min. The excess hydride was decomposed with a minimum amount of water and 2 N NaOH, and the dried ether layer was evaporated to dryness to yield a residue which was analyzed by GLC. The ratios between **13** and **14** are shown in Table I. Reactions of **1b** and **1c** with each salt carried out under the same conditions but stopping after relatively different contact times (1, 3, and 6 h for the reaction of **1b** with mercuric acetate, 15 min and 1 h for the reaction of **1b** with mercuric trifluoroacetate, 48 h for the reaction of **1c** with mercuric acetate, and 8 min and 3 h for the reaction of **1c** with mercuric trifluoroacetate) yielded the same product composition within experimental error. However, in the case of the reaction of **1b** with mercuric trifluoroacetate, much longer contact times (3 and 6 h) showed an increase of the percentage of the syn adduct due to a slow epimerization at the benzylic carbon.

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Registry No.—**6b** (X = CH_3COO), 64705-90-4; **6b** (X = CF_3COO), 64705-91-5; **6c** (X = CH_3COO), 64705-92-6; **6c** (X = CF_3COO), 64705-93-7; **9**, 5331-08-8; **10b**, 64705-94-8; **11b**, 64705-95-9; **17b**, 64705-96-0; **12c**, 64705-97-1; **13b**, 64705-98-2; **13c**, 64705-99-3; **14b**, 64706-00-9; **4a**, 64706-01-0; **15b**, 1821-23-4; **15c**, 27163-65-1 methylene iodide, 75-11-6; *p*-bromotoluene, 106-38-7; tosyl chloride, 98-59-9; 2-methylcyclohexanone, 583-60-8.

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Elimination of Tertiary α Hydrogens from Tosylhydrazones with Lithium Diisopropylamide: Preparation of Trisubstituted Alkenes

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Tosylhydrazones containing only tertiary α hydrogens react with lithium diisopropylamide (LDA) to yield trisubstituted alkenes. The reaction of these and other tosylhydrazones with LDA shows a high degree of regiospecificity which is controlled by the stereochemistry of the imino bond. The stereochemistry of the reaction is manifested by the dominance of the cis alkene except in cases where isomerization to the trans alkene has a low activation barrier. The reaction of LDA with tosylhydrazones of β-keto esters is also successful.

The reaction of tosylhydrazones with alkyllithium reagents is a convenient method of preparing terminal or disubstituted alkenes.[1] This reaction has not, however, proved to be useful for the preparation of trisubstituted alkenes. Although a few isolated examples of tertiary α-hydrogen elimination have been reported,[2,3] no yield or product distribution was given. We recently reported that isobutyrophenone tosylhydrazone does not undergo elimination with methyllithium in ether at 0 °,[1] but at room temperature substitution at the imino carbon competes effectively with elimination.[4] Although substitution can be inhibited by the use of tetramethylethylenediame (TMEDA) as a co-solvent, the yield of isobutenylbenzene is quite poor.

We now wish to report that trisubstituted alkenes are conveniently prepared from tosylhydrazones which contain only tertiary α hydrogens by the use of lithium diisopropylamide (LDA) instead of methyllithium.[5-7] The moderate product yields (38–66%) are compensated by the convenience and by the mild reaction conditions.[8] Table I shows the data for the production of five trisubstituted alkenes.

The data in Table I show that for products which do not tend to undergo isomerization, TMEDA is the solvent of choice. However, in systems which do tend to isomerize, TMEDA appears to facilitate the rearrangement. For example, 2-methyl-2-norbornene isomerizes to 2-methylenenorbornane,[9] and the tricyclic system behaves similarly. The low

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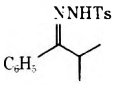
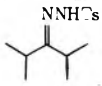
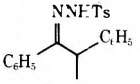
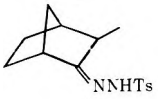
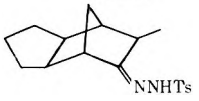
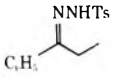
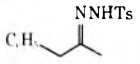
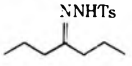
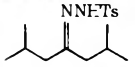
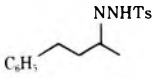
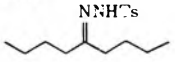
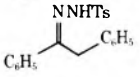
Table I. Trisubstituted Alkenes from Tosylhydrazones and Lithium Diisopropylamide

Tosylhydrazone	Registry no.	Solvent	Product(s)	Registry no.	Yield, %
	56638-11-0	TMEDA	Isobutenylbenzene	768-49-0	57[a]
	17530-00-6	TMEDA	2,4-Dimethyl-2-pentene	625-65-0	54[a]
	54288-47-0	TMEDA	1,2-Diphenyl-1-propene (cis/trans ratio, 16:84)		66[b]
	64884-74-8	Ether	2-Methyl-2-norbornene	694-92-8	38[b]
		TMEDA	2-Methyl-2-norbornene		81[c]
			3-Methylenenorbornene	497-35-8	19[c]
	64884-75-9	Ether	9-Methyltricyclo[5.2 $1.0^{2,6}$]-8-decene	64937-27-5	43[b]
		TMEDA	9-Methyltricyclo[5.2 $1.0^{2,6}$]-8-decene		32[b]
			9-Methylenetricyclo[5.2.1.$0^{2,6}$]-decane	64937-28-6	26[b]

[a] Product isolated by distillation. [b] Product isolated by column chromatography. [c] Ratio by gas chromatography.

Table II. Ratio of *cis*- and *trans*-Alkenes from Tosylhydrazones and LDA/TMEDA

Tosylhydrazone	Registry no.	Product	Registry no.	Cis/trans ratio	Yield, %
	17336-66-2	*trans*-1-Phenyl-1-propene	873-66-5		40[b]
	14195-24-5	*trans*-1-Phenyl-1-propene			40[a]
	36432-88-9	3-Heptene		92:8	55[b]
	64884-76-0	2,6-Dimethyl-3-heptene		92:8	74[b]
	64884-77-1	1-Phenyl-3-butene	768-56-9		75[b]
	64884-78-2	4-Nonene		94:6	72[b]
	19816-85-4	Stilbene		80:20	72[c]

[a] Yield obtained by GC standard method. [b] Product isolated by distillation. [c] Product isolated by column chromatography.

cis/trans ratio observed in the formation of 1,2-diphenyl-1-propene also appears to be the result of some isomerization since higher ratios were observed using ether solvent.[10] For this reason several other tosylhydrazones which would give stable products were tested with the LDA/TMEDA reactant. Table II shows the results of this investigation.

The exclusive formation of *trans*-1-phenyl-1-propene from propiophenone tosylhydrazone with LDA/TMEDA is in direct contrast with the 3:1 cis/trans ratio observed with MeLi/Et_2O.[10] The case of phenylacetone tosylhydrazone is even more striking since the allylbenzene product, obtained with MeLi/Et_2O,[1,4] is not observed at all. The other tosylhydrazones shown in the table give predominantly cis products, a result consistent with the previous observations.[10] From these data, it appears as if an especially active allylic hydrogen is required for product isomerization; whereas the bicyclic and tricyclic internal alkenes appear to be special cases.[9] This argument is supported by the exclusive formation of 1-phenyl-3-butene from 1-phenyl-3-butanone tosylhydrazone.

An explanation for the dominant formation of cis products comes from the recent reports on the stereoselective α-proton abstraction from oximes and their derivatives.[11-13] Scheme I depicts a reasonable mechanism based on the oxime results.

The tosylhydrazone syn dianion, which was proposed by us[4] and confirmed by Dauben,[14] can exist in conformation A or B. Since it appears that the stabilizing force in the dianion is the 6π-electron overlap,[13] it follows that the other nonbonding pair on nitrogen will be repelled and that the electropositive sulfur will be attracted by the electron density on the α carbon. Therefore, any group attached to the α carbon would prefer to be in conformation A. Alternatively, if the lone electron pair is "inside," it may sterically induce the substituent on the α carbon to reside preferentially on the "outside." In either event, the cis-alkene product would be generated.[15]

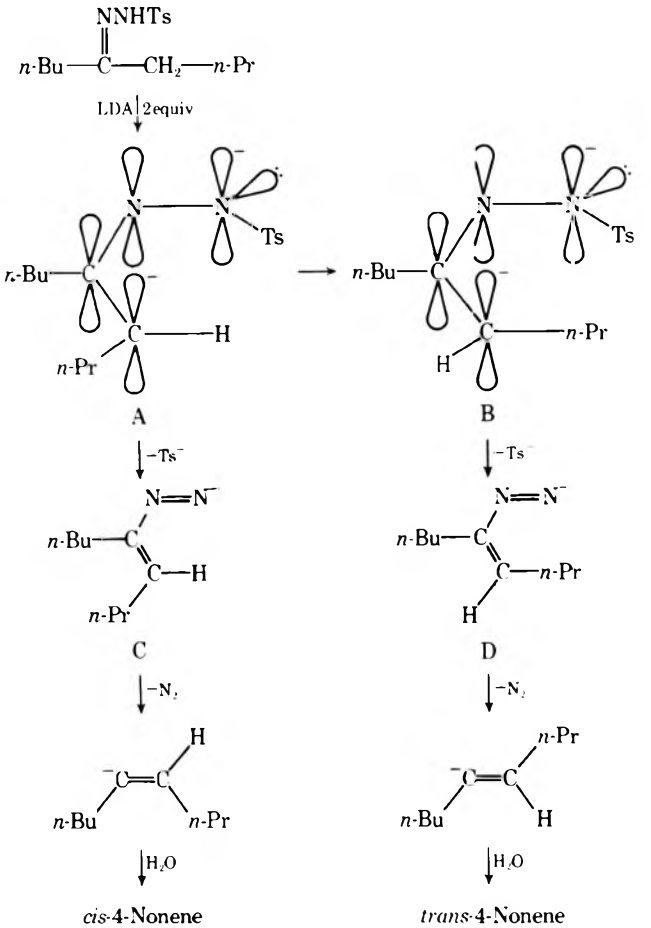
The case of 2-octanone tosylhydrazone represents an interesting example which again demonstrates that the stereochemistry of the carbon–nitrogen double bond controls the regiospecificity of the reaction.[4,14] Highly purified 2-octanone tosylhydrazone consists of a single stereoisomer, and it yields 1-octene exclusively upon reaction with alkyllithium reagents.[16,17] However, in some preparations of 2-octanone tosylhydrazone a second stereoisomer can be detected, albeit

Table III. Physical Constants for Tosylhydrazones

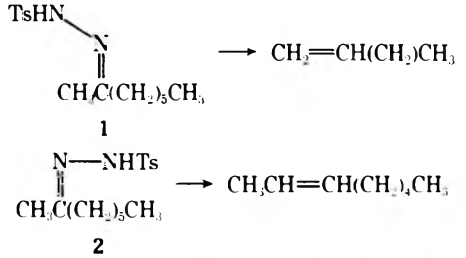
Tosylhydrazone of	Yield, %	Mp, °C	MS *m/e* (relative intensity)
Isobutyrophenone	84	103–104	316 (M^+, 6), 119 (100), 117 (42), 139 (29), 91 (29), 132 (26)
2,4-Dimethyl-3-pentanone	64	112–113	282 (M^+, 10), 127 (100), 97 (63), 41 (59), 91 (55), 55 (40)
1,2-Diphenyl-1-propanone	57	147–149	378 (M^+, 4), 223 (100), 91 (44), 105 (38), 194 (29), 179 (27)
3-Methyl-2-norbornanone	85	130–132	292 (M^+, 6), 137 (100), 91 (44), 95 (38), 93 (34), 79 (32)
9-Methyl-8-ketotricyclo-[5.2.1.$0^{2,6}$]decane	65	145–146	332 (M^+, 6), 177 (100), 79 (40), 91 (25), 109 (14), 41 (14)
1-Phenyl-2-propanone	93	137–139	302 (M^+, 7), 147 (100), 91 (67), 118 (48), 117 (35), 107 (30)
Propiophenone	96	120–121	302 (M^+, 9), 147 (100), 118 (62), 119 (60), 43 (50), 91 (43)
4-Heptanone	84	80–81	282 (M^+, 16), 127 (100), 44 (86), 42 (63), 41 (54), 43 (42)
5-Nonanone	81	66	310 (M^+, 8), 113 (100), 155 (80), 58 (80), 41 (54), 55 (50)
Deoxybenzoin	70	137–138	364 (M^+, 6), 91 (100), 92 (33), 65 (23), 209 (20), 180 (15)
2,6-Dimethyl-4-heptanone	76	110–112	310 (M^+, 10), 155 (100), 58 (65), 99 (60), 56 (60), 43 (50)
1-Phenyl-3-butanone	92	125–126	316 (M^+, 25), 91 (100), 161 (43), 117 (36), 131 (30), 57 (25)

[a] All mass spectra obtained at 70-eV ionizing energy.

Scheme I



in small amounts. In one preparation we were able to obtain a 76:24 mixture of the two stereoisomers as determined by ^1H NMR spectroscopy. The major isomer has a syn relationship between the methyl group and the tosylamide function (1), and the minor isomer has an anti relationship[18] (2). Decomposition of this stereoisomeric mixture with LDA in TMEDA yields a product mixture which contains a mixture of 1-octene and 2-octene in the ratio of 80:20 as determined by gas chromatography. These results are totally consistent with elimination of a syn α hydrogen in the alkene-forming reaction.



Experimental Section

Materials. Ketones, with the exception of 1,2-diphenyl-1-propanone, 3-methyl-2-norbornanone, and 9-methyl-8-ketotricyclo[5.2.1.$0^{2,6}$]decane, were obtained from commercial sources. 1,2-Diphenyl-1-propanone was prepared by phase-transfer alkylation of deoxybenzoin with methyl iodide.[13] 3-Methyl-2-norbornanone was prepared in 71% isolated yield by treating 2-norbornanone with LDA in THF/HMPA at −78 °C followed by reaction with methyl iodide. 9-Methyl-8-ketotricyclo[5.2.1.$0^{2,6}$]decane was prepared by generating the dianion of 8-ketotricyclo[5.2.1.$0^{2,6}$]decane tosylhydrazone and subsequent trapping with methyl iodide. Tosylhydrazine was prepared by treating tosyl chloride with hydrazine.[20] Tosylhydrazones were prepared in 70–95% isolated yield by treating the ketone with tosylhydrazine in 95% ethanol. Best results were obtained when ketones were purified prior to use. Methyllithium in diethyl ether was used to generate LDA and was purchased from Ventron Alfa Products. Diisopropylamine was dried over sodium hydroxide and distilled. Tetramethylethylenediamine (TMEDA) was dried over lithium aluminum hydride and distilled. Elimination reactions were carried out in two solvents, diethyl ether and TMEDA. Diethyl ether was employed to inhibit the isomerization of reactive alkene products. Yields were somewhat lower when diethyl ether was used as a solvent. In cases where alkenes were produced having the cis configuration, 10 equiv of diisopropylamine was employed per equivalent of tosylhydrazone. In all other cases 4 equiv of diisopropylamine were employed, from which 2.5 equiv of LDA was generated. Two workup procedures were employed to remove diisopropylamine and TMEDA from alkene products. One procedure employed aqueous acid washes. In the other, neutral conditions were obtained by first washing the organic phase with water to remove TMEDA, followed by several washes with copper sulfate solution to remove diisopropylamine. The later procedure can be used effectively with acid-sensitive alkenes. Each procedure is outlined below. All glassware was dried at 115 °C prior to use.

The structures of all tosylhydrazones and alkene products were assigned on the basis of their mass spectral, NMR, and IR characteristics. The assignment of the cis configuration to alkenes derived from compounds 1 and 2 was made by comparing their carbon-13 NMR chemical shift data to known literature values.[21] Mass spectral data was obtained on a Varian CH-5 mass spectrometer. ^1H NMR spectra were obtained on Varian A60-A and HA-100 NMR spectrometers. Carbon-13 NMR spectra were obtained on a JEOL PFT-100 spectrometer equipped with a Nicolet Model 1080 data system. IR spectra were obtained on a Perkin-Elmer 337 grating infrared spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected.

Isobutyrophenone Tosylhydrazone (1): General Procedure. Tosylhydrazine 13.9 g (74 mmol) was dissolved in 30 mL of hot 95% ethanol and isobutyrophenone (10.0 g, 67.5 mmol), and 3 drops of concentrated HCl was added. The solution was boiled for 10 min and cooled. The tosylhydrazone was crystallized and isolated, yield 18.0 g (84%); mp 103–104 °C; IR (KBr) 3200, 2950, 1600, 1340, 1160, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, 6), 2.46 (s, 3), 2.72 (septet, 1), 6.9–7.9 (m, 9); mass spectrum, see Table III.

Isobutenylbenzene: General Procedure A. Tosylhydrazones were eliminated by the following general procedure. Diisopropylamine (10.2 g, 101 mmol) and 51 mL of TMEDA (2 mL per millimole of tosylhydrazone) were placed in a 250-mL three-neck flask equipped with a magnetic stirrer, reflux condenser, solid addition tube, N_2 inlet, and drying tube. The solution was blanketed with N_2 gas and cooled to 0 °C. Methyllithium in diethyl ether (39.5 mL, 63.3 mmol) was added over a period of 5 min, and the solution was allowed to stir for 5 min. Isobutyrophenone tosylhydrazone (8.0 g, 25.3 mmol) was then added over a period of 3 min, the cold bath removed, and the solution stirred overnight at room temperature under an N_2 atmosphere. Enough water was carefully added to dissolve lithium salts. The solution was poured into a separatory funnel, the layers were separated, and the aqueous phase was extracted three times with 50 mL of diethyl ether. The organic layers were combined and washed five times with 50 mL of water. The resulting ether layer was washed with 50-mL aliquots of 0.48 M HCl until the aqueous layer maintained a pH of 0.3. The ether layer was washed once with 50 mL of saturated $NaHCO_3$ solution followed by one 50-mL water wash. The organic layer was dried over Na_2SO_4 and filtered, and the ether removed by fractional distillation. The alkene was then distilled to yield 1.9 g of 1-phenyl-2-methylpropene (57%), bp 103–104 °C (43 mm); IR (neat) 3100, 3000, 1650, 1600, 1450, 920, 840, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (s, 3), 1.84 (d, 3), 6.26 (m, 1), 7.22 (s, 5); mass spectrum (70 eV), *m/e* (relative intensity) 78 (8), 65 (12), 77 (12), 39 (14), 115 (35), 91 (37), 132 (M^+, 80), 117 (100).

2-Methyl-2-norbornene: General Procedure B. The following procedure inhibits the isomerization of alkene products. Sensitive alkene products are isolated under nonacidic conditions. Diisopropylamine (4.1 g, 40.8 mmol), TMEDA (2.4 g, 20.4 mmol), and 40 mL of anhydrous diethyl ether were placed in a 250-mL three-neck flask equipped with a magnetic stirrer, reflux condenser, solid addition tube, N_2 inlet, and drying tube. The solution was blanketed with N_2 gas and cooled to 0 °C. Methyllithium in diethyl ether (17.0 mL, 25.5 mmol) was added over a period of 5 min, and the resulting solution was allowed to stir for 15 min. 3-Methyl-2-norbornanone tosylhydrazone (3.0 g, 10.2 mmol) was added over a period of 3 min. The cold bath was removed, and the solution was stirred for 25 h at room temperature under an N_2 atmosphere. Enough water was carefully added to dissolve lithium salts. The solution was poured into a separatory funnel, the layers were separated, and the aqueous phase was extracted three times with 30 mL of diethyl ether. The organic extracts were combined and washed eight times with 30 mL of water. The organic phase was washed with 60-mL aliquots of 5% $CuSO_4$ solution until all the diisopropylamine had been removed; usually four washes are required. The $CuSO_4$ extracts were suction filtered to remove a pasty emulsion, and the resulting filtrate was extracted twice with 30 mL of diethyl ether. The organic extracts were combined and washed once with 20 mL of 5% $CuSO_4$ solution. All the ether extracts were combined, dried over Na_2SO_4, and filtered, and the diethyl ether was removed by fractional distillation. Residual traces of pentane were removed under a gentle stream of nitrogen to yield 2-methyl-2-norbornene, 0.4 g (38%); IR (neat) 2940, 1630, 1400, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–1.70 (m, 6), 1.72 (d, 3), 1.65 (s, 2), 5.50 (s, 1); mass spectrum (70 eV), *m/e* (relative intensity) 39 (14), 91 (18), 108 (M^+, 20), 79 (36), 80 (100).

2,4-Dimethyl-2-pentene. Following general procedure A for alkene preparation, 2,4-dimethyl-3-pentanone tosylhydrazone (8.0 g, 28.4 mmol) and 70.9 mmol of LDA in 57 mL of TMEDA yielded 1.5 g of 2,4-dimethyl-2-pentene (54%), bp 67–68 °C; IR (neat) 2950, 1675, 1470, 1380, 1030, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 6), 1.60 (d, 3), 1.63 (d, 3), 2.44 (broad septet, 1), 4.98 (broad d, 1); mass spectrum (70 eV), *m/e* (relative intensity) 53 (15), 67 (39), 84 (20), 56 (25), 98 (M^+, 28), 39 (45), 41 (65), 55 (79), 83 (100).

1,2-Diphenyl-1-propene. Following general procedure A for alkene preparation, 1,2-diphenyl-1-propanone tosylhydrazone (8.0 g, 21.2 mmol) and 53 mmol of LDA in 43 mL of TMEDA yielded 2.7 g of 1,2-diphenyl-1-propene (66%) after column chromatography through Al_2O_3 employing 100% pentane as the eluent, mp 77–79 °C; IR (KBr) 3020, 1630, 1590, 1480, 1440, 1380, 930, 875, 760, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (d, cis isomer, 3), 2.22 (d, trans isomer, 3), 6.78–7.63 (m, 10); mass spectrum (70 eV), *m/e* (relative intensity) 116 (10), 77 (12), 91 (14), 103 (16), 89 (15) 195 (16), 193 (19), 165 (20), 115 (29), 180 (37), 178 (54), 194 (96), 179 (100).

2-Methyl-2-norbornene and 2-Methylenenorbornane. Following general procedure A for alkene preparation, 3-methyl-2-norbornanone tosylhydrazone (3.0 g, 10.2 mmol) and 25.5 mmol of LDA in 20.4 mL of TMEDA yielded, after chromatography through Al_2O_3 using 100% pentane as the eluent, 0.6 g of a mixture of 2-methyl-2-norbornene and 2-methylenenorbornane (54%, 81:19). Each isomer was collected by preparative gas chromatography on a 10% SE-30 column ($^3/_8$ in × 16 ft). Each isomer was subsequently characterized. 2-Methyl-2-norbornene: IR (neat) 2940, 1630, 1400, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–1.70 (m, 6), 1.72 (d, 3), 1.65 (s, 2), 5.50 (s, 1); mass spectrum (70 eV), *m/e* (relative intensity) 39 (14), 91 (18), 108 (M^+, 20), 79 (36), 80 (100).

2-Methylenenorbornane: IR (neat) 2980, 1880, 1670, 1450, 910, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–2.25 (m, 8), 2.37 (s, 1), 2.70 (s, 1), 4.60 (s, 1), 4.85 (s, 1); mass spectrum (70 eV), *m/e* (relative intensity) 81 (10), 78 (14), 106 (20), 41 (30), 77 (31), 39 (34), 67 (38), 108 (M^+, 45), 80 (75), 66 (77), 79 (100).

9-Methyltricyclo[5.2.1.$0^{2,6}$]-8-decene and 9-Methylenetricyclo[5.2.1.$0^{2,6}$]decane. Following general procedure A for alkene preparation, 9-methyl-8-ketotricyclo[5.2.1.$0^{2,6}$]decane tosylhydrazone (3.0 g, 9.0 mmol) and 22.5 mmol of LDA in 18 mL of TMEDA yielded, after chromatography through Al_2O_3 using 100% pentane as the eluent, 0.7 g of 9-methyltricyclo[5.2.1.$0^{2,6}$]-8-decene and 9-methylenetricyclo[5.2.1.$0^{2,6}$]decane (58%, 55:45). Each isomer was separated and collected by preparative gas chromatography on a 10% SE-30 column and characterized. 9-Methyltricyclo[5.2.1.$0^{2,6}$]-8-decene: IR (neat) 2970, 2850, 1660, 1470, 1440, 1310, 1020, 810, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–2.48 (m, 12), 1.72 (d, 3), 5.60 (broad s, 1); mass spectrum (70 eV), *m/e* (relative intensity) 43 (10), 91 (13), 39 (14), 41 (14), 67 (15), 77 (15), 148 (M^+, 19), 81 (30), 79 (60), 80 (100).

9-Methylenetricyclo[5.2.1.$0^{2,6}$]decane: IR (neat) 2930, 2880, 1670, 1480, 1470, 1450, 1430, 1280, 1030, 920, 880, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.50 (m, 14), 4.57 (s, 1), 4.83 (s, 1); mass spectrum (70 eV), *m/e* (relative intensity) 93 (10), 133 (10), 66 (11), 106 (11), 39 (13), 105 (15), 78 (18), 41 (19), 77 (19), 81 (19), 91 (19), 67 (23), 148 (M^+, 35), 79 (76), 80 (100).

Gas Chromatographic Standardization of *trans*-1-Phenyl-1-propene vs. Bicyclohexyl. *trans*-1-Phenyl-1-propene (0.1021 g, 0.86 mmol) and 0.1400 g of bicyclohexyl were carefully weighed (Mettler balance) into a vial, and 3.0 mL of diethyl ether was then added. This mixture was subjected to the following gas chromatographic conditions: column, $^1/_8$ in × 8 ft. Dow Corning 550 on 80–100 mesh Chromosorb W; injector temperature, 230 °C; detector temperature, 260 °C; column temperature, 80 °C initial, 200 °C final; program rate, 8 °C/min; carrier gas rate (N_2), 50 mL/min; sample size, 15 μL. A series of three chromatograms were obtained from which a molar response factor of 1.026 was calculated (moles of bicyclohexyl vs. moles of *trans*-1-phenyl-1-propene).

***trans*-1-Phenyl-1-propene.** Following general procedure A for alkene preparation, phenylacetone tosylhydrazone (2.990 g, 9.87 mmol), bicyclohexyl (0.7612 g, 4.58 mmol), and 24.7 mmol of LDA in 20 mL of TMEDA were reacted for 23 h at room temperature. Reaction aliquots were removed after 7.5 h and subjected to the gas chromatographic conditions described above. A final reaction aliquot was removed and analyzed after 23 h of reaction time. Percent yield values were determined using the equation $M_x = A_xS_sM_s/A_sS_x$ and a molar response factor of $S_s/S_x = 1.026$ (M_x, moles of substrate; M_s, moles of standard; A_x, peak area of substrate; A_s, peak area of standard; S_x, response of substrate; S_s, response of standard). A 40% yield of *trans*-1-phenyl-1-propene was found to be produced after 7.5 h of reaction time. After 23 h of reaction time only a 20% yield of *trans*-1-phenyl-1-propene was present with no new products present in a gas chromatogram of the reaction mixture.

1-Phenyl-3-butene. Following general procedure A for alkene preparation, 1-phenyl-3-butanone tosylhydrazone (5.0 g, 15.8 mmol) and 39.5 mmol of LDA in 32 mL of TMEDA yielded 1.5 g of 1-phenyl-3-butene (75%), bp 51 °C (10 mm); IR (neat) 2950, 1625, 1580, 1480, 1440, 990, 910, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10–2.86 (m, 4), 4.80–5.20 (m, 2), 5.50–6.18 (m, 1), 7.15 (s, 1); mass spectrum (70 eV), *m/e* (relative intensity) 104 (10), 39 (12), 92 (14), 65 (19), 132 (M^+, 40), 91 (100).

1-Phenyl-1-propene. Following general procedure A for alkene preparation, propiophenone tosylhydrazone (5.0 g, 16.5 mmol) and 41.4 mmol of LDA in 66 mL of TMEDA yielded, after 3.0 h reaction time, 0.9 g of 1-phenyl-1-propene (48%), bp 47–48 °C (5.0 mm); IR (neat) 2920, 2850, 1650, 1580, 1480, 1410, 960, 805, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (d, 3), 5.90–6.60 (m, 2), 7.26 (m, 5); mass spectrum (70 eV), *m/e* (relative intensity) 63 (10), 65 (10), 77 (10), 78 (10), 103 (13), 51 (15), 39 (16), 91 (38), 116 (40), 118 (M^+, 93), 117 (100).

***cis*- and *trans*-3-Heptene.** Following general procedure A for alkene preparation, 4-heptanone tosylhydrazone (8.0 g, 28.4 mmol) and 71 mmol of LDA in 57 mL of TMEDA yielded 1.5 g of *cis*- and *trans*-3-heptene (55%; cis/trans ratio, 92:8 by ^{13}C NMR integration), bp 85–87 °C; IR (neat) 2900, 1650, 1450, 1360, 1060, 960, 890, 870, 790, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63–1.67 (m, 8), 1.67–2.33 (m, 4), 5.30 (m, 2); ^{13}C NMR data was collected and compared with literature

values[21] obtained on authentic samples of *cis*- and *trans*-3-heptene; mass spectrum (70 eV), *m/e* (relative intensity) 42 (16), 70 (17), 39 (20), 42 (20). 98 (M^+, 35), 55 (52), 69 (55), 56 (75), 41 (100).

***cis*- and *trans*-4-Nonene.** Following general procedure A for alkene preparation, 5-nonanone tosylhydrazone (7.0 g, 22.5 mmol) and 56.5 mmol of LDA in 45 mL of TMEDA yielded 2.0 g of *cis*- and *trans*-4-nonene (72%; cis/trans ratio, 94:6 by ^{13}C NMR integration), bp 135–137 °C; IR (neat) 2930, 1650, 1460, 1380, 1055, 970, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64–1.73 (m, 12), 1.73–2.30 (m, 4), 5.37 (m, 2); ^{13}C NMR data was collected and compared with literature values[21] obtained on authentic samples of *cis*- and *trans*-4-nonene; mass spectrum (70 eV), *m/e* (relative intensity) 57 (11), 67 (12), 97 (14), 83 (17), 84 (18), 42 (16), 43 (26), 69 (28), 126 (M^+, 30), 70 (38), 56 (51), 41 (60), 55 (100).

***cis*- and *trans*-Stilbene.** Following general procedure A for alkene preparation, deoxybenzoin tosylhydrazone (8.0 g, 21.8 mmol) and 54.8 mmol of LDA in 44 mL of TMEDA yielded 2.9 g of *cis*- and *trans*-stilbene after chromatography through alumina (72%). The cis/trans ratio was determined to be 80:20 by gas chromatography. GC conditions were the following: column, ⅛ in × 12 ft, 10% SE-30 (silicon rubber) on 80–100 mesh Chromosorb W; injector temperature, 230 °C; detector temperature, 260 °C; column temperature, 100 °C initial, 240 °C final; program rate, 4 °C/min; carrier gas rate (N_2), 50 mL/min; sample size, 5.0 μL (*cis*- and *trans*-stilbene are injected in chloroform solution). Retention times: *cis*-stilbene, 8 min 48 s; *trans*-stilbene, 10 min 12 s. The trans isomer was allowed to crystallize from the cis/trans mixture and was separated by suction filtration and washed with pentane. The cis isomer was isolated from the filtrate. *cis*-Stilbene: IR (neat) 3000, 2930, 1600, 1490, 1450, 925, 780, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (s, 2), 7.22 (s, 10); mass spectrum (70 eV), *m/e* (relative intensity) 77 (10), 177 (11), 76 (12), 89 (21), 165 (33), 178 (54), 179 (74), 180 (M^+, 100).

trans-Stilbene: IR (KBr) 3000, 1590, 1490, 1450, 970, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (s, 2), 7.39 (m, 10); mass spectrum (70 eV), *m/e* (relative intensity) 177 (10), 76 (14), 89 (19), 165 (30), 178 (50), 179 (74), 180 (M^+, 100).

***cis*- and *trans*-2,6-Dimethyl-3-heptene.** Following general procedure A for alkene preparation, 2,6-dimethyl-4-heptanone tosylhydrazone (8.0 g, 25.8 mmol) and 64.5 mmol of LDA in 52 mL of TMEDA yielded 2.4 g of *cis*- and *trans*-2,6-dimethyl-3-heptene (74%; cis/trans ratio, 92:8 by ^{13}C NMR integration), bp 119 °C; IR (neat) 2900, 1600, 1460, 1360, 1350, 1160, 1100, 1020, 970, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–1.05 (m, 12), 1.10–1.80 (septet, 1), 1.80–2.10 (m, 2), 2.25–2.90 (septet, 1), 4.95–5.40 (m, 2); ^{13}C NMR ($CDCl_3$) from proton-decoupled spectra (see structure I), 22.4 (C-7), 23.2 (C-1), 26.5

$$\overset{1}{(CH_3)_2}\overset{2}{C}\overset{3}{H}CH{=}\overset{4}{C}H\overset{5}{C}H_2\overset{6}{C}H(\overset{7}{C}H_3)_2$$

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(C-6), 28.7 (C-2, cis isomer), 31.2 (C-2, trans isomer), 36.6 (C-5, cis isomer), 41.8 (C-5, trans isomer), 126.1 (C-4, cis isomer), 137.7 (C-4, trans isomer), 138.1 (C-3, cis isomer), 138.8 ppm (C-3, trans isomer); mass spectrum (70 ev), *m/e* (relative intensity) 42 (12), 67 (13), 69 (20), 83 (23), 57 (31), 126 (M^+, 32), 70 (43), 43 (57), 41 (75), 56 (85), 69 (95), 55 (100).

1-Octene and *cis*- and *trans*-2-Octene. Following general procedure A for alkene preparation, 2-octanone tosylhydrazone (8.0 g, 27 mmol) and 70 mmol of LDA in 56 mL of TMEDA yielded 2.4 g of a mixture of 1-octene and *cis*- and *trans*-2-octene (80%), bp 110 °C; IR (neat) 2920, 1640, 1460, 1375, 1000, 910, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–2.30 (m, 13), 4.72–5.20 (m, 2), 5.30–6.20 (m, 1); 1-octene/*cis*-2-octene/*trans*-2-octene ratio, 80:10:10 by GC (GC conditions: column, ⅛ in × 12 ft, 10% SE-30 (silicone rubber) on 80–100 mesh Chromosorb W; injector temperature, 50 °C initial, 200 °C final; program rate, 4 °C/min; carrier gas rate (N_2), 50 mL/min; sample size, 5.0 μL); GC–MS was performed on the reaction mixture and found to be consistent with that obtained for authentic samples;[22] mass spectrum (70 eV), *m/e* (relative intensity) 1-octene, 112 (M^+, 10), 70 (62), 42 (73), 56 (87), 55 (87), 41 (92), 43 (100); *m/e* *cis*-2-octene, 112 (M^+, 19), 43 (21), 42 (53), 70 (51), 56 (53), 41 (95), 55 (100); *m/e* *trans*-2-octene, 112 (M^+, 24), 43 (19), 42 (44), 70 (49), 56 (65), 41 (91), 55 (100).

Registry No.—Isobutyrophenone, 611-70-1; 2,4-dimethyl-3-pentanone, 565-80-0; 1,2-diphenyl-1-propanone, 2042-85-5; 3-methyl-2-norbornanone, 643-51-6; 9-methyl-8-ketotricyclo-[5.2.1.$0^{2,6}$]decane, 64884-79-3; 1-phenyl-2-propanone, 103-79-7; propiophenone, 93-55-0; 4-heptanone, 123-19-3; 5-nonanone, 502-56-7; deoxybenzoin, 451-40-1; 2,6-dimethyl-4-heptanone, 108-83-8; 1-phenyl-3-butanone, 2550-26-7; tosylhydrazine, 1576-35-8; *cis*-1,2-diphenyl-1-propene, 1017-22-7; *trans*-1,2-diphenyl-1-propene, 833-81-8; *cis*-3-heptene, 7642-10-6; *trans*-3-heptene, 14686-14-7; *cis*-4-nonene, 10405-84-2; *trans*-4-nonene, 10405-85-3; *cis*-stilbene, 645-49-8; *trans*-stilbene, 103-30-0; *cis*-2,6-dimethyl-3-heptene, 20488-35-1; *trans*-2,6-dimethyl-3-heptene, 64884-80-6; 2-octanone tosylhydrazone, 54798-76-4; 1-octene, 111-66-0; *cis*-2-octene, 7642-04-8; *trans*-2-octene, 13389-42-9; 2-octanone, 111-13-7; lithium diisopropylamide, 4111-54-0.

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Regiospecific Synthesis of Homoallylic Alcohols from Tosylhydrazones

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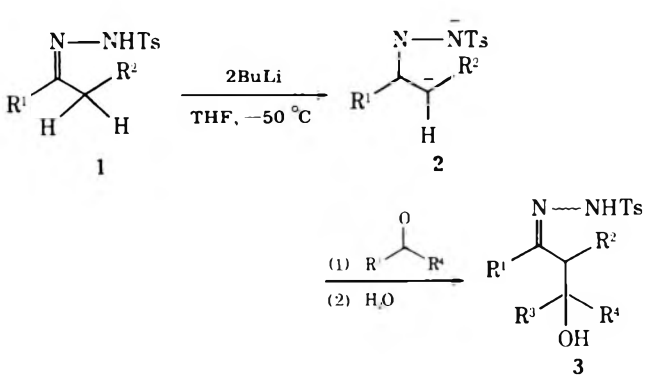
Regiospecifically generated tosylhydrazone dianions are trapped with aldehydes and ketones yielding β-hydroxytosylhydrazone dianions. Neutralization affords β-hydroxytosylhydrazones, which may be converted with or without isolation cleanly and in good yield to homoallylic alcohols upon treatment with alkyllithium reagents. A rationale is provided for the regiochemistry of this elimination. All attempts to obtain β-hydroxy ketones from the corresponding tosylhydrazone were unsuccessful.

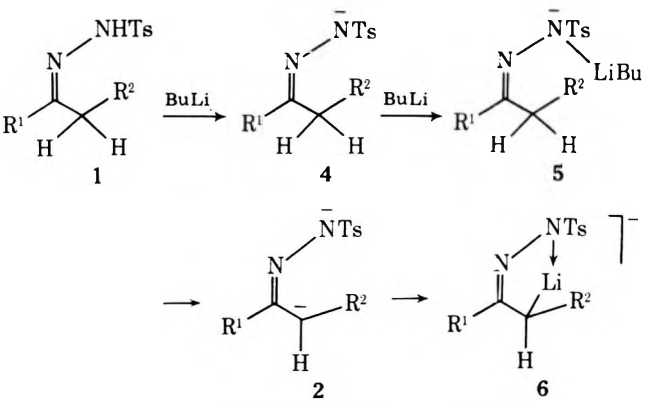
The formation of alkenes from tosylhydrazones and alkyllithium reagents,[1] or lithium diisopropylamide,[2] has proved to be a useful reaction. In the alkyllithium reaction, alkene formation is known to proceed via a syn dianion,[3] through a vinyldiimide anion,[3] and to a vinyl anion,[3,4] with subsequent protonation to give the product. It is also known that proton abstraction from solvent may occur,[5] and in favorable cases under the influence of excess base an allyl anion may be generated. The high cis/trans ratios previously observed in acyclic systems[6] coupled with the fact that a primary deuterium isotope effect is observed for the abstraction of a syn α proton (7.5 ± 2.2 determined for pinacolone tosylhydrazone-α-*d* by mass spectrometry) point to an E1cB mechanism for the elimination reaction. We now wish to report that the syn dianion is readily trapped on carbon with aldehydes and ketones, yielding β-hydroxytosylhydrazones (**3**) after protonation (Scheme I).

Our initial report concerning the regiochemistry of dianion formation[3] has been followed by much work in similar systems which also produce syn dianions upon treatment with alkyllithium reagents.[7-9] Tosylhydrazones lacking α protons undergo reductive alkylation,[10] as do aldehyde tosylhydrazones.[11] The enhanced acidity of the syn α protons in oximes[7,8] has been attributed to the chelation effect[12,13] and a 6π electron nonbonded through space interaction.[14] Since the observed regiochemistry of proton abstraction in both oximes and tosylhydrazones is a result of kinetic control, we feel that the intermediate nitrogen monoanion (**4**, Scheme II) is exerting a directional effect on the incoming second equivalent of alkyllithium reagent. It is well-known that heteroatoms, by virtue of their nonbonding electron pairs, may direct lithium bases to a nearby site via a transient coordinated species (**5**). The dianion is reluctant to invert configuration, which strongly suggests that it is present as the internally coordinated metallocycle (**6**). For instance, phenylacetone tosylhydrazone yields allylbenzene in the elimination reaction.[3] Internally coordinated metallocyclic intermediates have ample precedent,[7,8,13-15] and their formation has been proposed only in systems which bear a 1,4 relationship between heteroatom and the carbon bearing the incipient negative charge.

Scheme I



Scheme II



The regiochemistry of tosylhydrazone dianion formation toward the less hindered side of the imino carbon has been found to be a general phenomenon, and since a strong steric bias exists in the formation of tosylhydrazones from unsymmetrical ketones, the route ketone → tosylhydrazone → dianion represents a convenient method for the regiospecific generation of enolate equivalents. In order to further test the regioselectivity of dianion formation, a symmetrical system, dibenzyl ketone tosylhydrazone, was chosen for study. The 60-MHz ^{1}H NMR spectrum of this tosylhydrazone ($CDCl_3$) shows the methylene signals separated by 10 Hz. Conversion to dianion (>2 equiv of *n*-butyllithium, THF, 0 °C)[16] followed by quenching with D_2O affords the α-deuteriotosylhydrazone (>97% labeled by MS) in 83% yield. The 60-MHz ^{1}H NMR spectrum indicates that deuteration has occurred, within the limits of detection, only on the upfield methylene group. Similar results have been obtained at −78 °C with acetone tosylhydrazone. That the upfield signal in the ^{1}H NMR spectrum corresponds to the syn α protons may be inferred from the 60-MHz ^{1}H NMR spectra ($CDCl_3$) of the series of tosylhydrazones of acetone, 2-butanone, 3-methyl-2-butanone, and pinacolone, the methyl absorptions of which are displayed in Table I. The assignments of syn and anti (entries 2, 3, and 4) are in accord with the known isomer ratios for the corresponding oximes.[17]

Further support for the syn regiospecificity of dianion formation comes from the deuteration of a syn/anti mixture (83:17) of 2-butanone tosylhydrazone. Conversion to the dianion (>2 equiv of *n*-butyllithium, THF, −50 °C) followed by D_2O quenching yields a mixture of labeled tosylhydrazones. Mass spectral analysis indicates that the mixture is labeled 81% on methyl and 19% on methylene.

Our preliminary report[3] indicated that tosylhydrazone dianions may be trapped with alkyl halides and that a large steric requirement accompanies dianion formation. Oxime dianions behave similarly.[7,8] In view of the fact that attempts to trap tosylhydrazone dianions with secondary alkyl halides were unsuccessful, a large steric requirement must also be present in the reaction of the electrophile with the dianion,

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Table I

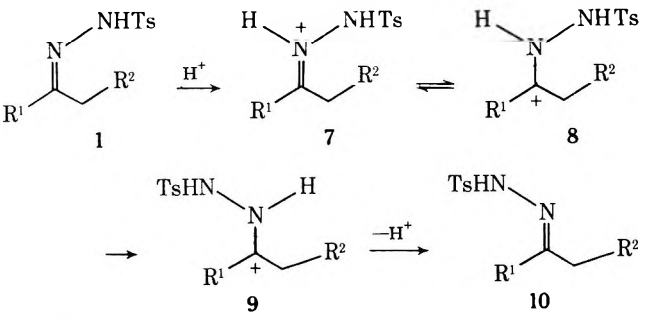
Tosylhydrazone of (syn/anti)	^{1}H NMR absorption, δ *syn*-α-Methyl	*anti*-α-Methyl
(1) Acetone (50:50)	1.80	1.92
(2) 2-Butanone (83:17)	1.80	1.92
(3) 3-Methyl-2-butanone (>92:<8)	1.80	1.92
(4) Pinacolone (100:0)	1.75	

and it is consistent with syn dianion formation. That the alkylated tosylhydrazone obtained upon treatment of cyclohexanone tosylhydrazone dianion with methyl iodide bears an anti relationship for tosylamido and methyl groups and is identical to the tosylhydrazone made from the treatment of 2-methylcyclohexanone with tosylhydrazine in hot acidic ethanol may be explained in terms of an acid-catalyzed isomerization during the isolation procedure (Scheme III.)

Acetone tosylhydrazone dianion yields an equilibrium mixture (syn/anti, 83:17) of 2-butanone tosylhydrazone in 67% yield when trapped with methyl iodide and subjected to neutral isolation. Also, dibenzyl ketone tosylhydrazone-*syn*-α-*d* quickly isomerizes upon treatment with dilute mineral acid to a mixture of syn- and anti-labeled material. Such isomerization has not been reported for oximes.

Tosylhydrazone dianions formed at −50 °C with *n*-butyllithium in THF when trapped with aldehydes and ketones afford β-hydroxytosylhydrazones in good to excellent yield as shown in Table II. We anticipated that based on the demonstrated regiospecificity of dianion formation (vida supra) such a reaction would provide a convenient modified crossed-aldol reaction since published procedures are available for the regeneration of ketones from tosylhydrazones.[18-20] Unfortunately, all attempts to generate β-hydroxy ketones

Scheme III



from β-hydroxytosylhydrazones resulted in a retro-aldol reaction under acidic conditions or no reaction under basic conditions. Other routes to effect this seemingly facile conversion are currently under investigation.

However, treatment of β-hydroxytosylhydrazones with >3 equiv of alkyllithium reagent results in their smooth elimination at room temperature. For instance, acetophenone tosylhydrazone may be converted to the dianion at −50 °C and trapped with acetone to give 1-phenyl-3-hydroxy-3-methyl-1-butanone tosylhydrazone. Elimination of this β-hydroxytosylhydrazone with alkyllithium reagent leads to 1-phenyl-3-hydroxy-3-methyl-1-butene (cis and trans) in 76% yield.

The preferred regiochemistry of elimination in these systems, however, was found to be away from oxygen to form the homoallylic alcohol, as the data in Table III demonstrates. The uniformly good yields, regiospecificity, convenience, and ready availability of starting materials, as well as the apparent paucity of reliable methods for the generation of homoallylic alcohols,[21-24] prompted this report.

It appears that the steric factors which govern the regiochemistry of dianion formation, and hence elimination, in tosylhydrazones are not operative in β-hydroxytosylhydra-

Table II. β-Hydroxytosylhydrazones from Tosylhydrazones[a]

Tosylhydrazone of	Electrophile	Product (tosylhydrazone of)	Yield, %	Mp (dec), °C
Acetone	Acetone	2-Hydroxy-2-methyl-4-pentanone	57	134.0–135.5
	Propionaldehyde	4-Hydroxy-2-hexanone	78	131.5–132.0
2-Butanone	Acetone	2-Hydroxy-2-methyl-4-hexanone	61	130.5–132.5
	Propionaldehyde	5-Hydroxy-3-heptanone	74	132.0–133.0
Cyclohexanone	Acetone	2-(2-Hydroxy-2-propyl)cyclohexanone	79	153.5–155.0
	Propionaldehyde	2-Propyl(1-hydroxy)cyclohexanone	74	138.0–141.0
Phenylacetone	Acetone	1-Phenyl-4-hydroxy-4-methyl-2-pentanone[b]	80	128.0–130.0
	Propionaldehyde	1-Phenyl-4-hydroxy-2-hexanone	77	136.5–138.0
Acetophenone	Acetone	1-Phenyl-3-hydroxy-3-methyl-1-butanone	80	134.0–137.0

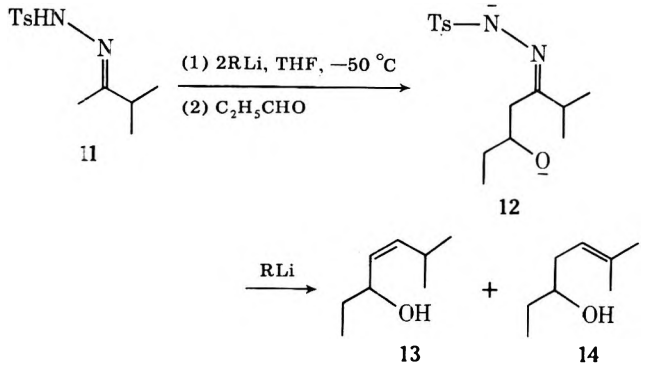
[a] All β-hydroxytosylhydrazones had spectral data consistent with the assigned structure (see Experimental Section). [b] This was the only compound obtained as a single isomer; all others were syn/anti mixtures by NMR.

Table III. Homoallylic Alcohols[a] from Tosylhydrazones[b]

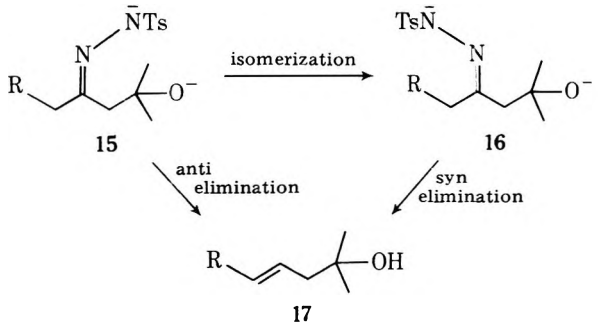
Tosylhydrazone of	Electrophile	Product	Yield, %	Bp,[c] °C
Acetone	Acetone	2-Hydroxy-2-methyl-4-pentene	49	60 (15)
	Propionaldehye	4-Hydroxy-1-hexene	48	60 (12)
2-Butanone	Acetone	2-Hydroxy-2-methyl-4-hexene (cis and trans)	75	60 (7.0)
	Propionaldehyde	5-Hydroxy-2-heptene (cis and trans)	73	43 (5.0)
Cyclohexanone	Acetone	3-(2-Propyl-2-hydroxy)-1-cyclohexene	65	76–78 (4.5)
	Propionaldehyde	3-(1-Hydroxy-1-propyl)-1-cyclohexene	66	77–79 (3.5)
Phenylacetone	Acetone	1-Phenyl-4-hydroxy-4-methyl-1-pentene (cis/trans, 11:89)	59	95 (1.0)
	Propionaldehyde	1-Phenyl-4-hydroxy-1-hexene (cis/trans, 15:85)	43	87–89 (0.3)

[a] All homoallylic alcohols had spectral data consistent with the assigned structure (see Experimental Section). [b] The intermediate β-hydroxytosylhydrazones were not isolated [c] Pressures are indicated in parentheses.

Scheme IV



Scheme V



zones. Although β-branching effects cannot be ruled out from the above series of β-hydroxytosylhydrazones, elimination of 2-methyl-5-hydroxy-3-heptanone tosylhydrazone dianion (12, Scheme IV) should produce allylic alcohol 13 in a sterically controlled reaction. In fact, elimination of this dianion (generated in situ by trapping 3-methyl-2-butanone tosylhydrazone dianion with aceteldehyde) with methyllithium leads to a 1.0:1.1 mixture of allylic alcohol 13 and homoallylic alcohol 14. Since the tertiary side of both tosylhydrazones[3] and oximes[7,8] is reluctant to form a syn dianion, it appears that the elimination of β-hydroxytosylhydrazones may involve the abstraction of an anti α proton. Such an interpretation is not unreasonable in view of the fact that the negatively charged oxygen atom should by the inductive effect decrease the acidity of the syn α protons. Although an isomerization to form 16 under the reaction conditions has not been ruled out, it seems unlikely in view of the results obtained for elimination of 12 above, and those of Kofron.[7] The possible elimination pathways are depicted in Scheme V. Although a concerted elimination involving the generation of a trianion intermediate may be envisioned, no trianion has been trapped, and no evidence is presented for its formation.

We also wish to report that chloroformates make excellent traps for tosylhydrazone dianions. For example, cyclopentanone tosylhydrazone is converted via the dianion and trapping with ethyl chloroformate into the corresponding ethyl ester in 76% yield. Since lithium diisopropylamide is effective in tosylhydrazone eliminations in the presence of ester functions,[2] this method appears to be promising for the production of β,γ-unsaturated esters.

Experimental Section

Materials. Tosylhydrazine was conveniently prepared according to the procedure of Friedman.[25] Ketones were purchased from commercial suppliers and used without purification. *n*-Butyllithium was purchased as pentane solutions from Ventron and stored at −5 °C. Methyllithium was purchased from Ventron as ethereal solutions and stored at ambient temperature. Reagent grade tetrahydrofuran was purchased from Mallinckrodt and distilled from lithium aluminum hydride prior to use. D_2O was purchased from Merck. Acetone was distilled from $KMnO_4$ prior to use in the trapping experiments. Propionaldehyde was distilled prior to use. Reactions were carried out under a stream of dry nitrogen in glassware oven-dried at 140 °C overnight.

Instrumentation. All analytical gas chromatography analyses were done on a Varian Aerograph instrument (FID). Preparative gas chromatography work was done on a Varian 1600 instrument using a 6 ft × 0.25 in. 8% DC-550 column. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. ^1H NMR spectra were obtained with either a Varian A-60A instrument or a Varian T-60. Mass spectra were obtained on a Varian CH-5 mass spectrometer at 70-eV ionizing energy. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Procedures. Tosylhydrazones: General Procedure. In a 50-mL Erlenmeyer flask, tosylhydrazine (9.3 g, 50 mmol) is dissolved in 20 mL of ethanol containing 1 drop of concentrated HCl on a steam bath. The flask is allowed to cool briefly, the ketone (50 mmol) is added, and the flask is swirled and heated for 1 min. After cooling to room temperature, the flask is cooled to −15 °C in the freezer, and the colorless crystals are isolated by suction filtration. Recrystallization from ethanol affords the tosylhydrazone in 78–95% yield.

β-Hydroxytosylhydrazones: General Procedure. The tosylhydrazone (10 mmol) is dissolved in 50 mL of THF in a 100-mL two-neck round-bottom flask protected from moisture and equipped with a rubber serum cap and magnetic stirrer. The solution is cooled to −50 °C by means of a dry ice/2-propanol bath and titrated to pale yellow with 10 mmol of *n*-butyllithium solution. An additional 10 mmol of *n*-butyllithium solution is added, the orange to deep red solution is allowed to stir for 1 min, and 11 mmol of acetone or propionaldehyde is added neat. The color bleaches immediately, and the pale yellow to colorless solution is allowed to warm with stirring to room temperature. It is then treated with 25 mL of 10% HCl and salted, the layers are separated, and the aqueous phase is extracted with 25 mL of THF. The combined organic extracts are dried ($MgSO_4$), and the solvent is removed on the rotory evaporator, leaving pale yellow crystals. The crude material is recrystallized from warm aqueous ethanol.

Homoallylic Alcohols: General Procedure. In a 100-mL two-neck round-bottom flask protected from moisture and equipped with a magnetic stirrer, reflux condenser, and rubber serum cap is placed 10 mmol of the tosylhydrazone and 50 mL of THF. The solution is cooled to −50 °C by means of a dry ice/2-propanol bath and is titrated to pale yellow with 10 mmol of *n*-butyllithium solution. An additional 10 mmol of *n*-butyllithium solution is added, the orange to deep red solution is allowed to stir for 1 min, and the mixture is then quenched with acetone or propionaldehyde. After warming to room temperature, 20 mmol of methyllithium solution is added, and the orange solution is allowed to stir for 6.0 h at room temperature. Hydrolysis is effected with dilute HCl at 0 °C, and the aqueous phase is saturated with salt and extracted with three 10-mL portions of THF. The combined organic phase is extracted with two 16-mL portions of 1 M NaOH, saturated with salt, washed with brine, and concentrated to ~5 mL by flash evaporation. The product is obtained by chromatography on alumina or by distillation.

Spectral data for the β-hydroxytosylhydrazones are as follows ("exchanges" refers to protons exchangeable with D_2O).

2-Hydroxy-2-methyl-4-pentanone tosylhydrazone: ^1H NMR ($CDCl_3$, Me_4Si) δ 1.11, 1.23 (6 H, pair of s), 1.87, 1.93 (3 H, pair of s), 2.33–2.53 (3 H, m, 1 exchanges), 2.42 (3 H, s), 7.20–8.00 (5 H, m, 1 exchanges); IR (film) 3325, 3000, 2840, 1600, 1565, 1310, 1145, 935, 810, 720 cm^{-1}; MS *m/e* (relative intensity) 284 (M^+, 1), 157 (7), 111 (8), 139 (9), 91 (23), 31 (28), 226 (36), 59 (59), 71 (100).

4-Hydroxy-2-hexanone tosylhydrazone: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.89 (3 H, t, J = 7 Hz), 1.13–1.61 (2 H, m), 1.83, 1.91 (3 H, pair of s), 2.18–2.49 (2 H, m), 2.41 (3 H, s), 2.84 (1 H, s, exchanges), 3.50–3.93 (1 H, m), 7.15–7.96 (5 H, m, 1 exchanges); IR (film) 3340, 3000, 2800, 1660, 1570, 1325, 1155, 1075, 920, 840, 815, 700 cm^{-1}; MS *m/e* (relative intensity) 284 (M^+, 1), 92 (10), 157 (10), 111 (16), 41 (19), 46 (22), 91 (25), 226 (27), 45 (33), 43 (35), 59 (52), 31 (56), 71 (100).

2-Hydroxy-2-methyl-4-hexanone tosylhydrazone: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.98 (3 H, t, J = 7.5 Hz), 1.15 (6 H, s), 2.13 (2 H, q, J = 7.5 Hz), 2.35 (3 H, s), 2.35 (2 H, s), 3.45 (1 H, s, exchanges), 7.27 (2 H, d, J = 8 Hz), 7.90 (2 H, d, J = 8 Hz), 7.92 (1 H, broad s, exchanges); IR (film) 3300, 2950, 2880, 1610, 1565, 1355, 1305, 1150, 940, 810, 755, 705 cm^{-1}; MS *m/e* (relative intensity) 298 (M^+, 2), 125 (4), 143 (6), 59 (7), 139 (8), 157 (9), 240 (23), 91 (28), 85 (100).

5-Hydroxy-3-heptanone tosylhydrazone: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.89 (3 H, t, J = 7.5 Hz), 0.99 (3 H, t, J = 7 Hz), 1.43 (2 H, broad q, J = 7 Hz), 2.03–2.52 (4 H, m), 2.41 (3 H, s), 3.22 (1 H, s, exchanges), 3.74 (1 H, m), 7.20 (2 H, d, J = 8 Hz), 7.75 (2 H, d, J = 8 Hz),

7.78 (1 H, s, exchanges); IR (film) 3490, 3100, 2980, 1660, 1595, 1315, 1160, 910, 815, 700 cm^{-1}; MS *m/e* (relative intensity) 298 (M^{+}, <1), 157 (10), 226 (12), 92 (13), 39 (16), 59 (16), 65 (18), 67 (18), 70 (18), 41 (30), 42 (33), 91 (34), 43 (51), 71 (64), 111 (100).

2-(2-Hydroxy-2-propyl)cyclohexanone tosylhydrazone: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.16, 1.31 (6 H, pair of s), 1.16–2.51 (8 H, m), 2.41 (3 H, s), 2.86 (1 H, t, J = 6 Hz), 3.04 (1 H, s, exchanges), 7.06–8.04 (5 H, m, 1 exchanges); IR (film) 3320, 2850, 1575, 1550, 1310, 1155, 1025, 955, 810, 700 cm^{-1}; MS *m/e* (relative intensity) 324 (M^{+}, <1), 112 (9), 266 (11), 81 (12), 41 (13), 67 (16), 91 (16), 43 (22), 31 (25), 151 (81), 111 (100).

2-Propyl(1-hydroxy)cyclohexanone tosylhydrazone: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.90, 1.00 (3 H, pair of t, J = 7 Hz), 1.10–2.65 (10 H, m), 2.43 (3 H, s), 2.82 (1 H, broad t), 3.02 (1 H, s, exchanges), 3.67 (1 H, m), 7.12–8.14 (5 H, m, 1 exchanges); IR (film) 3400, 2900, 2810, 1650, 1575, 1325, 1160, 1030, 815, 705 cm^{-1}; MS *m/e* (relative intensity) 324 (M^{+}, <1), 112 (9), 139 (11), 67 (15), 41 (16), 266 (16), 81 (18), 91 (19), 151 (20), 154 (29), 31 (34), 111 (100).

1-Phenyl-4-hydroxy-4-methyl-2-pentanone tosylhydrazone: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.14 (6 H, s), 2.31 (2 H, s), 2.43 (3 H, s), 3.06 (1 H, s, exchanges), 3.47 (2 H, s), 6.95–7.97 (10 H, m, 1 exchanges); IR (film) 3300, 2870, 2750, 1700, 1570, 1300, 1145, 1040, 810, 740, 695 cm^{-1}; MS *m/e* (relative intensity) 360 (M^{+}, 2), 31 (13), 115 (13), 92 (15), 65 (17), 187 (17), 43 (18), 117 (24), 118 (29), 130 (31), 302 (37), 59 (76), 91 (87), 147 (100).

1-Phenyl-4-hydroxy-2-hexanone tosylhydrazone: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.90 (3 H, broad t, J = 7 Hz), 1.45 (2 H, broad q, J = 7 Hz), 2.37 (3 H, s), 2.81 (2 H, broad s), 2.90 (2 H, d, J = 6.5 Hz), 3.18 (1 H, s, exchanges), 3.82 (1 H, broad t, J = 6.5 Hz), 7.20–8.06 (10 H, m, 1 exchanges); IR (film) 3320, 2950, 2850, 1560, 1540, 1310, 1150, 1065, 930, 810, 750, 690 cm^{-1}; MS *m/e* (relative intensity) 360 (M^{+}, 4), 191 (13), 59 (14), 53 (15), 172 (15), 39 (17), 41 (17), 129 (19), 131 (20), 115 (22), 105 (29), 92 (30), 67 (34), 61 (35), 176 (38), 104 (39), 79 (46), 103 (64), 173 (75), 91 (90), 133 (100).

1-Phenyl-3-hydroxy-3-methyl-1-butanone tosylhydrazone: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.20 (6 H, s), 2.42 (3 H, s), 2.93 (2 H, s), 3.03 (1 H, s, exchanges), 7.17–8.06 (9 H, m, 1 exchanges); IR (film) 3450, 3100, 3000, 1600, 1340, 1170, 1090, 910, 820, 805, 760, 695 cm^{-1}; MS *m/e* (relative intensity) 346 (M^{+}, 3), 152 (10), 105 (11), 132 (11), 78 (12), 134 (14), 173 (22), 65 (24), 77 (25), 288 (26), 92 (39), 59 (47), 91 (47), 103 (50), 104 (50), 43 (54), 133 (100).

Spectral data for the homoallylic alcohols are as follows.

4-Hydroxy-4-methyl-1-pentene: ^{1}H NMR (CCl_4, Me_4Si) δ 1.17 (6 H, s) 2.12 (1 H, s, exchanges), 2.18 (2 H, broad d, J = 7 Hz), 4.92 (1 H, m), 5.18 (1 H, m), 5.50–6.27 (1 H, m); MS *m/e* (relative intensity) 100 (M^{+}, <1), 41 (6), 71 (10), 57 (14), 43 (20), 44 (39), 42 (83), 59 (100).

4-Hydroxy-1-hexene: ^{1}H NMR (CCl_4, Me_4Si) δ 0.91 (3 H, t, J = 7 Hz), 1.12–1.71 (2 H, m), 2.18 (2 H, broad t), 3.33 (1 H, s, exchanges), 3.50 (1 H, m), 4.73–5.23 (2 H, m), 5.50–6.21 (1 H, m); IR (film) 3200, 2950, 2800, 1710, 1430, 1100, 955, 910, 775 cm^{-1}; MS *m/e* (relative intensity) 100 (M^{+}, <1), 58 (4), 60 (4), 28 (6), 42 (9), 57 (10), 71 (10), 39 (11), 27 (12), 29 (12), 43 (14), 41 (31), 31 (46), 59 (100).

5-Hydroxy-5-methyl-2-hexene (cis and trans): ^{1}H NMR (CCl_4, Me_4Si) δ 1.13, 1.17 (6 H, pair of s), 1.25 (2 H, s), 1.62 (3 H, d, J = 6 Hz), 2.04–2.30 (2 H, m), 3.30 (1 H, s, exchanges), 5.37–5.68 (2 H, m); IR (film) 3300, 2900, 1640, 1450, 1365, 1145, 1080, 1050, 965, 905, 780 cm^{-1}; MS *m/e* (relative intensity) 114 (M^{+}, <1), 79 (5), 42 (7), 60 (8), 99 (8), 53 (9), 96 (10), 55 (17), 39 (18), 56 (21), 81 (23), 41 (32), 43 (65), 59 (100).

5-Hydroxy-2-heptene (cis and trans): ^{1}H NMR (CCl_4, Me_4Si) δ 1.08 (3 H, t, J = 7 Hz), 1.23 (2 H, m), 1.54–1.78 (3 H, m), 2.13 (2 H, q, J = 7 Hz), 3.42 (1 H, s, exchanges), 3.25–3.71 (1 H, m), 5.35–5.67 (2 H, m); IR (film) 3350, 2900, 1650, 1460, 1360, 1045, 1025, 960, 900, 780, 680 cm^{-1}; MS *m/e* (relative intensity) 114 (M^{+}, <1), 39 (5), 51 (5), 54 (5), 41 (6), 45 (6), 81 (6), 58 (8), 87 (8), 53 (10), 67 (12), 38 (20), 69 (22), 85 (23), 55 (27), 57 (35), 43 (37), 56 (80), 40 (87), 59 (100).

3-(2-Propyl-2-hydroxy)-1-cyclohexene: ^{1}H NMR (CCl_4, Me_4Si) δ 1.10, 1.15 (6 H, pair of s), 1.18–2.35 (6 H, m), 3.13 (1 H, s, exchanges), 3.23–3.79 (1 H, m), 5.75 (2 H, m); IR (film) 3250, 2830, 1620, 1420, 1360, 1140, 1040, 950, 910, 890, 825, 765, 720 cm^{-1}; MS *m/e* (relative intensity) 140 (M^{+}, 1), 53 (5), 81 (5), 107 (5), 122 (5), 31 (6), 82 (6), 54 (7), 41 (9), 79 (10), 67 (13), 59 (100).

3-(1-Hydroxy-1-propyl)-1-cyclohexene: ^{1}H NMR (CCl_4, Me_4Si) δ 0.94 (3 H, t, J = 7 Hz), 1.11–2.40 (8 H, m), 3.13 (1 H, s, exchanges), 3.02–3.93 (2 H, m), 5.77 (2 H, m); IR (film) 3250, 2830, 1620, 1440, 1110, 965, 930, 875, 780, 720 cm^{-1}; MS *m/e* (relative intensity) 140 (M^{+}, <1), 66 (5), 83 (5), 93 (5), 122 (5), 65 (6), 68 (6), 80 (7), 44 (8), 51 (8), 57 (11), 77 (11), 55 (13), 79 (17), 81 (17), 53 (19), 54 (49), 59 (63), 52 (82), 67 (100).

1-Phenyl-4-hydroxy-4-methyl-1-pentene (cis and trans): ^{1}H NMR (CCl_4, Me_4Si) δ 1.17 (6 H, s), 2.45 (2 H, dd, J = 7, 2 Hz), 3.05 (1 H, exchanges), 5.57–6.67 (2 H, m), 7.23 (5 H, s); IR (film) 3300, 2900, 1625, 1580, 1555, 1480, 1365, 1130, 1070, 1020, 945, 910, 760, 695 cm^{-1}; MS *m/e* (relative intensity) 176 (M^{+}, <1), 119 (6), 129 (7), 116 (8), 39 (9), 128 (9), 158 (10), 41 (13), 91 (15), 115 (18), 143 (19), 117 (29), 43 (33), 118 (59), 59 (100).

1-Phenyl-4-hydroxy-1-hexene (cis and trans): ^{1}H NMR (CCl_4, Me_4Si) δ 0.78 (3 H, t, J = 7 Hz), 1.30 (2 H, m), 2.19 (2 H, broad q), 3.19 (1 H, s, exchanges), 3.35 (1 H, m), 6.17 (2 H, m), 7.05 (5 H, m); IR (film) 3400, 2950, 2750, 1625, 1560, 1300, 1140, 1000, 935, 900, 810, 760, 700 cm^{-1}; MS *m/e* (relative intensity) 78 (5), 43 (5), 129 (6), 105 (6), 51 (7), 57 (8), 105 (10), 77 (10), 41 (10), 119 (11), 116 (11), 176 (M^{+}, 12), 31 (15), 115 (18), 91 (20), 59 (33), 117 (53), 118 (100).

Cyclopentanone Tosylhydrazone. In a 50-mL Erlenmeyer flask, tosylhydrazine (9.3 g, 50 mmol) was dissolved in 20 mL of ethanol containing 1 drop of concentrated HCl on a steam bath. The flask was allowed to cool briefly, and 4.2 g (50 mmol) of cyclopentanone was added and the flask swirled. Vigorous boiling occured, and on cooling to room temperature a colorless precipitate formed. Further cooling in the freezer followed by suction filtration afforded 12.7 g (94%) of cyclopentanone tosylhydrazone: mp 180–184 °C dec; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.75 (4 H, m), 2.22 (4 H, m), 2.45 (3 H, s), 7.33 (2 H, d, J = 8 Hz), 7.75 (1 H, broad s), 7.92 (2 H, d, J = 7 Hz); MS *m/e* (relative intensity) 140 (10), 157 (10), 53 (14), 252 (M^{+}, 16), 80 (17), 65 (18), 68 (21), 91 (32), 96 (34), 41 (38), 67 (56), 97 (100).

2-Carboethoxycyclopentanone Tosylhydrazone. Cyclopentanone tosylhydrazone (1.26 g, 5.0 mmol) was dissolved in 25 mL of THF in a 50-mL two-neck round-bottom flask protected from moisture and equipped with a reflux condenser, rubber serum cap, and magnetic stirrer. The solution was cooled to −50 °C by means of a dry ice/2-propanol bath, and 5.0 mL (10 mmol) of a 2.0 M solution of *n*-butyllithium in pentane was added slowly with a syringe. After ~1 min of stirring, the red solution was treated with 0.55 g (5 mmol) of freshly distilled ethyl chloroformate, the cold bath removed, and the yellow solution allowed to stir for 30 min. Neutralization with dilute HCl, salting, and separation of the layers were followed by extraction of the aqueous phase with THF (3 × 10 mL). Drying ($MgSO_4$) and removal of the solvent on the rotoevaporator afforded a yellow oil which on recrystallization from ethanol/water yielded 1.22 g (76%) of 2-carboethoxycyclopentanone tosylhydrazone (syn/anti mixture) as pale yellow crystals, mp 134–135 °C dec. Major isomer [minor isomer]: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.23 [1.17], (3 H, t, J = 7 Hz), 1.50–2.83 (7 H, m), 2.45 (3 H, s), 4.12 [4.09] (2 H, d, J = 7 Hz), 6.80–8.24 symmetrical complex (4 H, m), 8.45 (1 H, broad s); MS *m/e* (relative intensity) 251 (5), 140 (6), 122 (7), 139 (8), 141 (9), 124 (10), 155 (11), 43 (12), 121 (12), 168 (13), 80 (16), 65 (17), 324 (M^{+}, 20), 95 (25), 41 (26), 91 (28), 67 (79), 123 (99), 169 (100).

Registry No.—Acetone tosylhydrazone, 3900-79-6, (*E*)-2-butanone tosylhydrazone, 62460-90-6; (*Z*)-2-butanone tosylhydrazone, 62460-91-7; (*E*)-3-methyl-2-butanone tosylhydrazone, 64884-92-0; (*Z*)-3-methyl-2-butanone tosylhydrazone, 64884-93-1; (*Z*)-pinacolone tosylhydrazone, 64884-94-2; 2-butanone tosylhydrazone, 4031-16-7; cyclohexanone tosylhydrazone, 4545-18-0; phenylacetone tosylhydrazone, 14195-24-5; acetophenone tosylhydrazone, 4545-21-5; propionaldehyde, 123-38-6; (*E*)-2-hydroxy-2-methyl-4-pentanone tosylhydrazone, 64884-95-3; (*Z*)-2-hydroxy-2-methyl-4-pentanone tosylhydrazone, 64884-96-4; (*E*)-4-hydroxy-2-hexanone tosylhydrazone, 64884-97-5; (*Z*)-4-hydroxy-2-hexanone tosylhydrazone, 64884-98-6; (*E*)-2-hydroxy-2-methyl-4-hexanone tosylhydrazone, 64884-99-7; (*Z*)-2-hydroxy-2-methyl-4-hexanone tosylhydrazone, 64885-00-3; (*E*)-5-hydroxy-3-heptanone tosylhydrazone, 64885-01-4; (*Z*)-5-hydroxy-3-heptanone tosylhydrazone, 64885-02-5; (*E*)-2-(2-hydroxy-2-propyl)cyclohexanone tosylhydrazone, 64885-03-6; (*Z*)-2-(2-hydroxy-2-propyl)cyclohexanone tosylhydrazone, 64885-04-7; 2-propyl(1-hydroxy)cyclohexanone tosylhydrazone, 64885-05-8; 1-phenyl-4-hydroxy-4-methyl-2-pentanone tosylhydrazone, 64885-06-9; (*E*)-1-phenyl-4-hydroxy-2-hexanone tosylhydrazone, 64885-07-0; (*Z*)-1-phenyl-4-hydroxy-2-hexanone tosylhydrazone, 64885-08-1; (*E*)-1-phenyl-3-hydroxy-3-methyl-1-butanone tosylhydrazone, 64885-09-2; (*Z*)-1-phenyl-3-hydroxy-3-methyl-1-butanone tosylhydrazone, 64884-85-1; 2-hydroxy-2-methyl-4-pentene, 624-97-5; 4-hydroxy-1-hexene, 688-99-3; (*Z*)-2-hydroxy-2-methyl-4-hexene, 19639-96-4; (*E*)-2-hydroxy-2-methyl-4-hexene, 19639-97-5; (*Z*)-5-hydroxy-2-heptene, 64884-86-2; (*E*)-5-hydroxy-2-heptene, 64884-87-3; 3-(2-propyl-2-hydroxy)-1-cyclohexene, 5723-91-1; 3-(1-hydroxy-1-propyl)-1-cyclohexene, 64884-88-4; (*Z*)-1-phenyl-4-hydroxy-4-methyl-1-pentene, 64884-89-5; (*E*)-1-phenyl-4-hydroxy-4-methyl-1-pentene, 55552-33-0; (*Z*)-1-phenyl-4-hydroxy-1-hex-

ene, 54985-30-7; (*E*)-1-phenyl-4-hydroxy-1-hexene, 54985-35-2; tosylhydrazine, 1576-35-8; 3-methyl-2-butanone, 563-80-4; pinacolone, 75-97-8; acetone, 67-64-1; 2-butanone, 78-93-3; cyclohexanone, 108-94-1; phenylacetone, 103-79-7; acetophenone, 98-86-2; cyclopentanone, 120-92-3; cyclopentanone tosylhydrazone, 17529-98-5; ethyl chloroformate, 541-41-3; (*Z*)-2-carboethoxycyclopentanone tosylhydrazone, 64884-90-8; (*E*)-2-carboethoxycyclopentanone tosylhydrazone, 64884-91-9.

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Studies on Selective Preparation of Aromatic Compounds. 15. The Lewis Acid Catalyzed Transalkylation of Some *tert*-Butyldiphenylmethanes and -ethanes in Aromatic Solvents[1]

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The Lewis acid catalyzed transalkylation of *tert*-butyl derivatives of diphenylmethanes (**2a–f**) and -ethanes (**25a–g**) in benzene or toluene was carried out under various conditions. It was found in the transalkylation of **2** that the $AlCl_3$–CH_3NO_2 catalyzed transbenzylation with trans-*tert*-butylation was observed and the $TiCl_4$ transbenzylation of electron-rich *tert*-butyldiphenylmethanes having highly steric crowdedness such as 2,2′,6,6′-tetramethyl- (**2d**) and 2,2′,3,3′-tetramethyldiphenylmethane (**2f**) took place without trans-*tert*-butylation. However, no $AlCl_3$–CH_3NO_2 catalyzed transalkylation of **25** was observed and only trans-*tert*-butylation in benzene took place to afford the desired 2,2′-dimethyl-(**27b**), 2,2′-diethyl-(**27c**), 2,2′-dimethoxy-(**27d**), 2,2′,3,3′-tetramethyl-(**27e**), and 2,2′,6,6′-tetramethyldiphenylethane (**27f**). Based on the above result it could be concluded that *tert*-butyl group can be used as a positional protective group for the preparation of some diphenylethanes but not diphenylmethanes.

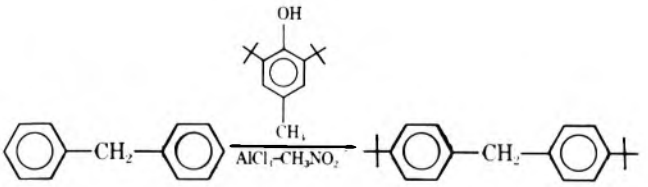
Although $AlCl_3$–CH_3NO_2 does not catalyze the transbenzylation and isomerization of diphenylmethanes,[2-8] it catalyzes transbenzylation of some 4,4′-dihydroxydiphenylmethane derivatives in toluene as was recently reported.[9]

We undertook the present study to obtain more detailed information about factors influencing the above novel transbenzylation of diphenylmethanes and in general to gain a better understanding of the mechanism of transalkylation.

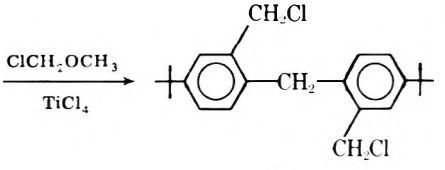
Results and Discussion

Preparation of Some *tert*-Butyldiphenylmethanes. The $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylation of diphenylmethane (**1**) with 2,6-di-*tert*-butyl-*p*-cresol[10] afforded 4,4′-di-*tert*-butyldiphenylmethane (**2a**) in good yield. 4,4′-Di-*tert*-butyl-2,2′-dimethyldiphenylmethane (**2b**) was prepared from **2a** via **3**. The chloromethylation of 4-*tert*-butyltoluene (**4a**) and 5-*tert*-butyl-1,3-dimethyl- (**4b**) and 4-*tert*-butyl-1,2-dimethylbenzene (**4c**) afforded the corresponding 5-*tert*-butyl-2-methyl- (**5a**), 4-*tert*-butyl-2,6-dimethyl- (**5b**), and 5-*tert*-butyl-2,3-dimethylbenzyl chloride (**5c**), respectively, in good yields.

In the $TiCl_4$ catalyzed benzylation of **4a, 4b,** and **4c** with the chlorides, 5,5′-di-*tert*-butyl-2,2′-dimethyl- (**2c**), 4,4′-di-*tert*-butyl-2,2′,6,6′-tetramethyl- (**2d**), 4,5′-di-*tert*-butyl-



1 2a



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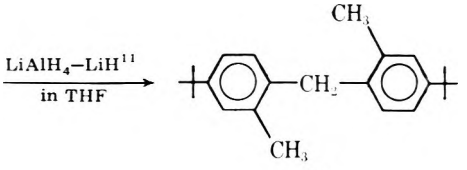
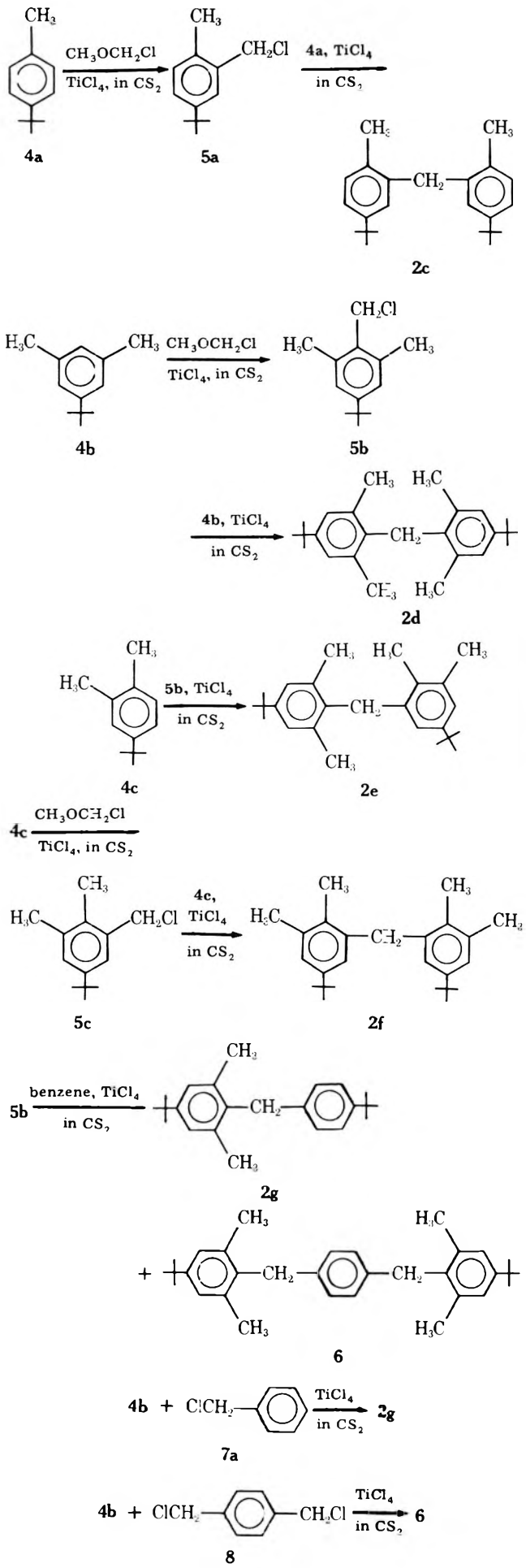


2b

Scheme I

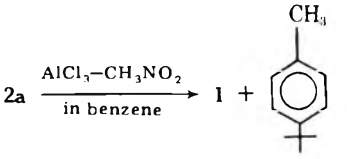


2,2′,3′,6-tetramethyl- (**2e**), and 5,5′-di-*tert*-butyl-2,2′,3,3′-tetramethyldiphenylmethane (**2f**) were obtained in good yields (Scheme I).

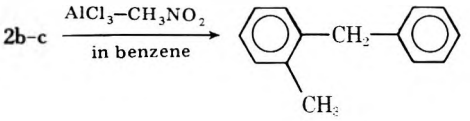
However, the expected product, 4-*tert*-butyl-2,6-dimethyldiphenylmethane (**2g**), in the benzylation of benzene with **5b** was formed in only 43% yield with formation of 1,4-bis(4-*tert*-butyl-2,6-dimethylbenzyl)benzene (**6**) in 50% yield even in excess benzene.

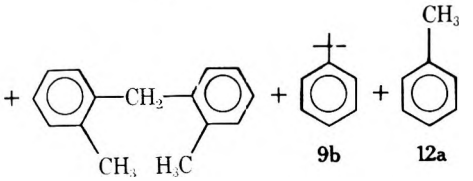
The compounds **2g** and **6** were also obtained by the $TiCl_4$ catalyzed benzylation of **4b** with benzyl chloride (**7a**) and 1,4-bis(chloromethyl)benzene (**8**) in 93 and 60% yields, respectively.

Transalkylation of 2. The Lewis acid catalyzed transalkylation of **2** was carried out under various conditions and the results are summarized in Table I. The *tert*-butyl group is transferred from **2a** to toluene.



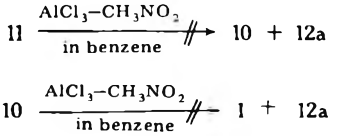
This result suggests that the trans-*tert*-butylation occurred selectively without the transbenzylation as expected from the previous papers.[2-8] However, the $AlCl_3$–CH_3NO_2 catalyzed transalkylation of **2b** and **2c** in benzene afforded 2-methyldiphenylmethane (**10**) and toluene (**12a**) besides the expected products 2,2′-dimethyldiphenylmethane (**11**) and *tert*-butylbenzene (**9b**). These results show clearly that the transbenzylation and trans-*tert*-butylation of **2b** and **2c** took place simultaneously to afford **10** and **11**.





The latter compound **11** seems to be the intermediate in the formation of the former **10** and **12a**.

However, when **11** or **10** was treated under same conditions, only the starting compound **10** or **11** was recovered in quantitative yield.



Although intermediates **13** and **14** could not be isolated when **2b** and **2c** were transalkylated, the reaction pathways in Scheme II might be proposed.

In fact, the $AlCl_3$–CH_3NO_2 catalyzed reaction of **14b**, which was prepared by the benzylation of **4a** with 2-methylbenzyl chloride (**7b**), afforded **10** and **11** in 81.1 and 10.3% yields.

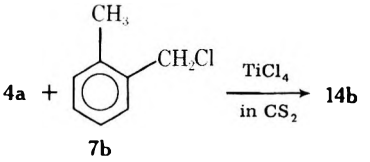
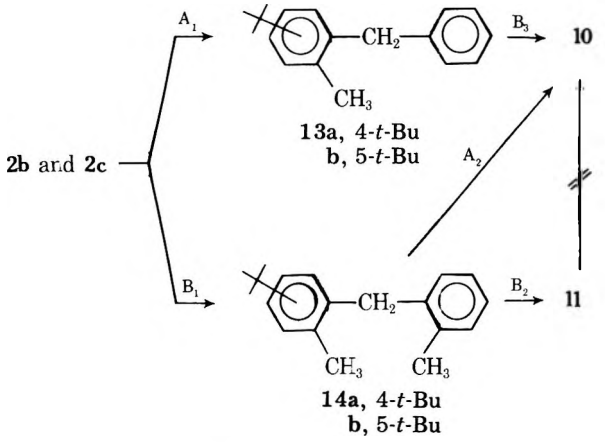


Table I. The Lewis Acid Catalyzed Transalkylation of 2[a]

Run	Substrate	Catalyst[b]	Solvent	Time, h	Product (%)[c]
1	**2a**	A	Toluene	3	**1** (100), **9a** (100)
2	**2a**	B	Toluene	3	No reaction
3	**2b**	A	Benzene	0.5	**10** (75), **11** (25), **9b** (100), **12a** (75)
4	**2b**	B	Benzene	3	No reaction
5	**2c**	A	Benzene	0.5	**10** (40), **11** (60), **9b** (100), **12a** (75)
6	**2c**	B	Benzene	3	No reaction
7	**2d**	A	Benzene	3	**16** (80), **1** (20), **9b** (100), **12b** (80)
8	**2d**	B	Benzene	3	**2g** (89), **4b** (77)
9	**2d**	B	Toluene	2	**18** (93), **4b** (95), **9a** (90)
10	**2d**	B	*m*-Xylene	0.5	**19** (99), **4b** (90)
11	**2d**	C	Toluene	5	No reaction
12	**2d**	C	*m*-Xylene	5	No reaction
13	**2e**	B	Benzene	3	**21** (73), **2g** (23), **4b** (70), **4c** (30)
14	**2f**	A	Benzene	3	**22** (75), **9b** (80), **12b** (78)
15[d]	**2f**	B	Benzene	3	**21** (20), **23** (40), **9a** (38), **4b** (22), **1** (+)[e]
16	**2g**	A	Benzene	1.5	**16** (88), **1** (12), **9b** (100)
17	**14b**	A	Benzene	1	**11** (81), **10** (10), **9b** (100), **12a** (10)
18	**21**	A	Benzene	1.5	**22** (97), **1** (3), **9b** (100)

[a] Reaction temperature, 50 °C; solvent/**2**, 30 mol/l mol; catalyst/**2**, 0.2 mol/l mol. [b] A, $AlCl_3$–CH_3NO_2; B, $TiCl_4$; C, $SnCl_4$. [c] The yields were determined by GC analyses. [d] **2f** was recovered in 40% yield. [e] Plus sign (+) means a trace amount (<1%).

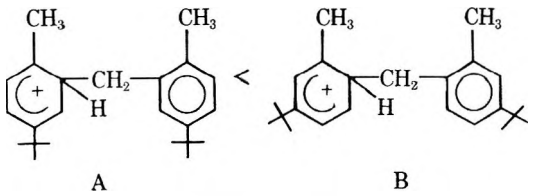
Scheme II



A: transbenzylation
B: trans-*tert*-butylation

The $AlCl_3$–CH_3NO_2 catalyzed transalkylation of **2b** afforded **10** and **11** in 75 and 25% yields, but the reaction of **2c** gave the same products in different yields, that is, 40 and 60% yields, respectively.

The relative rate of transbenzylation of **2b** and **2c** might be dependent upon the relative stabilities of the corresponding α complex A and B. The latter complex might be more stable than the former one.

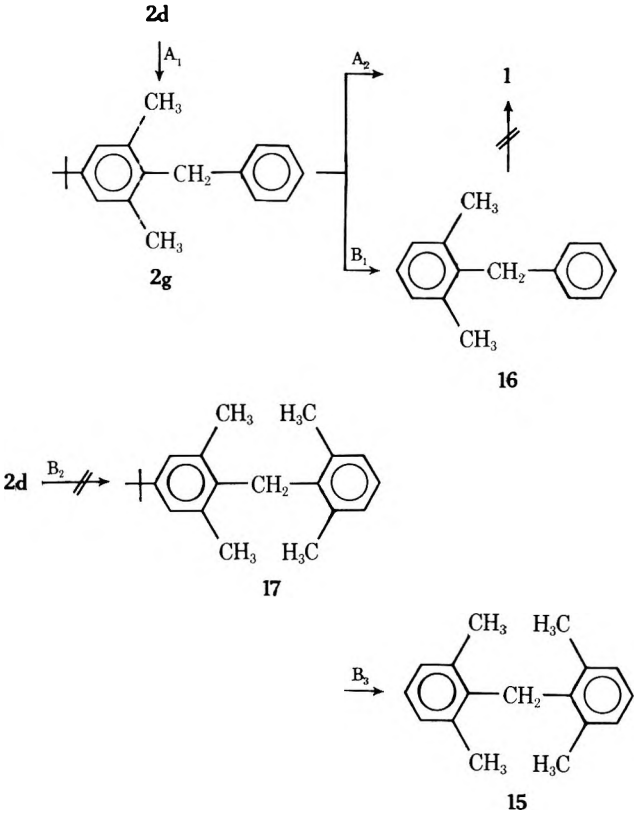


A B

In the $AlCl_3$–CH_3NO_2 catalyzed transalkylation of **2d** in benzene, an expected product, 2,2′,6,6′-tetramethyldiphenylmethane (**15**), was not obtained, but 2,6-dimethyldiphenylmethane (**16**), **1**, **9b**, and *m*-xylene (**12b**) were formed.

The transalkylation of **2g** in benzene afforded **1** and **16** in 20 and 80% yields. However, when **16** was treated with the catalyst only starting material was recovered. Based on the above results the reaction pathways in Scheme III are proposed.

Scheme III



A: transbenzylation
B: trans-*tert*-butylation

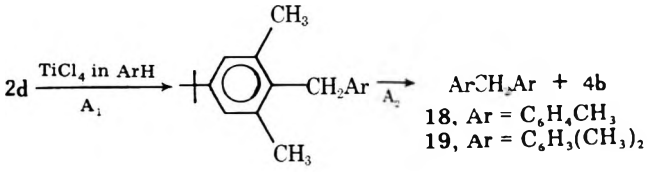
At the first step, transbenzylation (A_1) rather than the trans-*tert*-butylation (B_2) might selectively take place to afford **2g**, which gave **1** by the second transbenzylation (A_2) and **16** by the trans-*tert*-butylation (B_1), respectively. The former reaction (A_2) was less predominant than the latter reaction (B_1).

In contrast to the case of **2a**, **2b**, and **2c**, the $TiCl_4$ catalyzed transalkylation of **2d** in benzene afforded, surprisingly, only **2g** and **4b** in good yields.

$$\mathbf{2d} \xrightarrow[\text{in benzene}]{TiCl_4} \mathbf{2g} + \mathbf{4b}$$

This finding means that only the transbenzylation (A_1) of **2d** occurred selectively without the trans-*tert*-butylation (B_2) under the conditions used, and it also seems to support the proposed reaction pathway of Scheme III.

However, $SnCl_4$ did not show any activity for the transalkylation of **2d**. When toluene and *m*-xylene were used in place of benzene as a solvent and acceptor of alkyl groups in the $TiCl_4$ catalyzed transalkylation of **2d**, ditolylmethanes (**18**) and 2,2′,4,4′-tetramethyldiphenylmethane (**19**) were obtained in good yields, respectively.



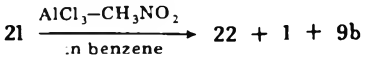
20

In these cases, not only the first-step transbenzylation (A_1) but also the second one (A_2) might easily occur, since toluene and *m*-xylene are stronger Lewis bases than benzene.

In the $TiCl_4$ catalyzed transbenzylation of **2e**, the formation of **2g** and 5-*tert*-butyl-2,3-dimethyldiphenylmethane (**21**) might be expected (Scheme IV). In fact, the reaction afforded **21**, **4b**, **2g**, and **4c** in 73, 27, 70, and 30% yields. The above result suggests that the transbenzylation A_1 was a more predominant reaction than the A_2, probably because the A_1 should reduce the steric hindrance of **2e** to a higher degree than A_2 should.

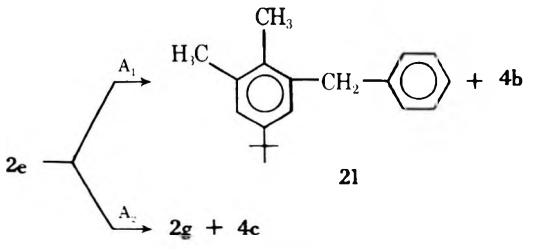
When **2f** was treated with $AlCl_3$–CH_3NO_2 catalyst in benzene, 2,3-dimethyldiphenylmethane (**22**) was obtained in 75% yield with a small amount of **1**.

The $AlCl_3$–CH_3NO_2 catalyzed transalkylation of **21** in benzene afforded **22**, **1**, and **9b** in 97.3, 2.7, and 100% yields, respectively.

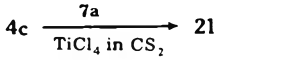


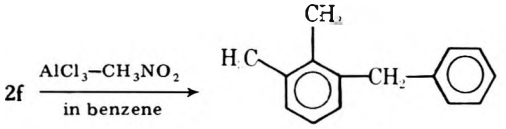
The $TiCl_4$ catalyzed transalkylation of **2f**, as well as **2d** and **2e**, afforded a transbenzylated product **21** and **4b**. However, a considerable amount of **2f** was recovered and the unexpected

Scheme IV

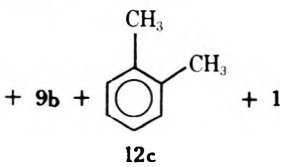


A: transbenzylation



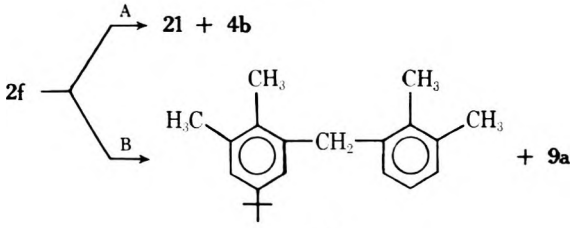


22



12c

Scheme V



23

A: transbenzylation
B: trans-*tert*-butylation

product, 5-*tert*-butyl-2,2′,3,3′-tetramethyldiphenylmethane (**23**), was also obtained in a low yield (Scheme V).

The crowdedness of the methyl groups of **2f** seems to be less than that of **2d** and **2e**. Consequently the above results might indicate that the steric factor should strongly influence the ease of the transbenzylation of diphenylmethanes.

The results obtained in the above transalkylation of **2** seem to strongly support the mechanisms proposed[9] previously for the transalkylation of 4,4′-dihydroxydiphenylmethanes.

Preparation of *tert*-Butyldiphenylethane (25). The *tert*-butyldiphenylethanes (**25b–g**) with the exception of 4,4′-di-*tert*-butyldiphenylethane (**25a**) were prepared by the coupling reaction[12] using CH_3MgI reagent and the corresponding benzyl chlorides (**5a–g**) (Scheme VI). In some coupling reactions, besides the expected product **25**, *tert*-butylethylbenzenes (**26**) were formed as byproducts. The yields of **25** and **26** are summarized in Table II.

Only **25a** was prepared by the $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylation of diphenylethane (**24**) with 2,6-di-*tert*-butyl-*p*-cresol according to the previously reported method.[10]

The Transalkylation of 25. The Lewis acid catalyzed transalkylation of **25** (Scheme VII) was carried out under various conditions and the results are summarized in Table III.

The $AlCl_3$–CH_3NO_2 and $TiCl_4$ catalyzed transalkylation of **25a** in toluene afforded **24** and 4-*tert*-butyltoluene (**9a**) in good yields. The former catalyst was active for the trans-*tert*-butylation of **2a**, but not the latter one as described above.

The result of the $TiCl_4$ catalyzed trans-*tert*-butylation of **25a** might suggest that the basicity of **25a** should be stronger than that of **2a**.

In contrast to both catalysts, $AlCl_3$ afforded a small amount of ditolylethane (**28**), **24a**, benzene (**12d**), and **9a** with a large amount of resinous material and unidentified compounds.

The result might indicate that $AlCl_3$ was too strong to use as a catalyst for the preparation of **27**. The $AlCl_3$–CH_3NO_2 catalyzed transalkylation of **25b** afforded the expected products **27b** and **9b** in good yields, while the corresponding diphenylmethane derivative gave trans-*tert*-butylated and transbenzylated products as previously described.

Table II. The Coupling Reaction of 1 Using CH_3MgI Reagent in Ether Solution[a]

Run	Chloride	Product (%)
1	**5a**	**25b** (72), **26b** (13)
2	**5d**	**25c** (87), **26c** (17)
3	**5e**	**25d** (63), **26d** (20)
4	**5c**	**25e** (75), **26e** (0)
5	**5b**	**25f** (89), **26f** (11)
6	**5f**	**25g** (70), **26g** (0)
7	**5g**	**25h** (71), **26h** (0)

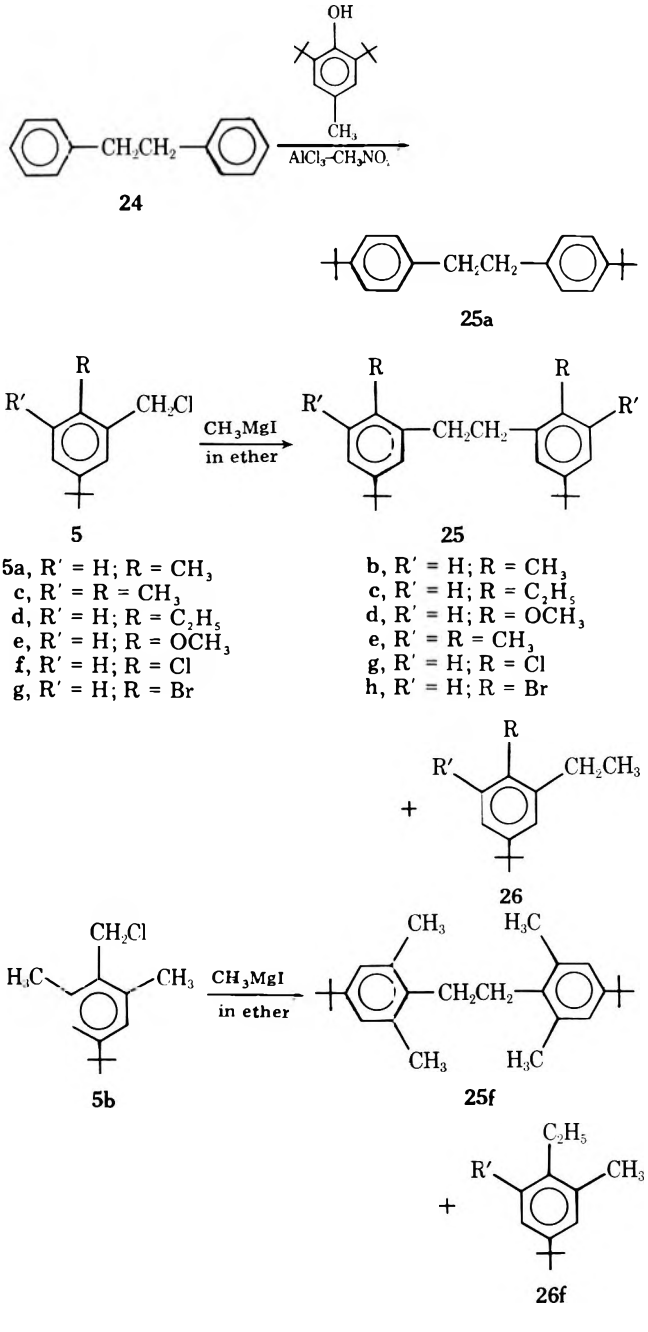
[a] Reaction temperature, reflux; reaction time, 1 h.

Table III. The Lewis Acid Catalyzed Transalkylation of 25[a]

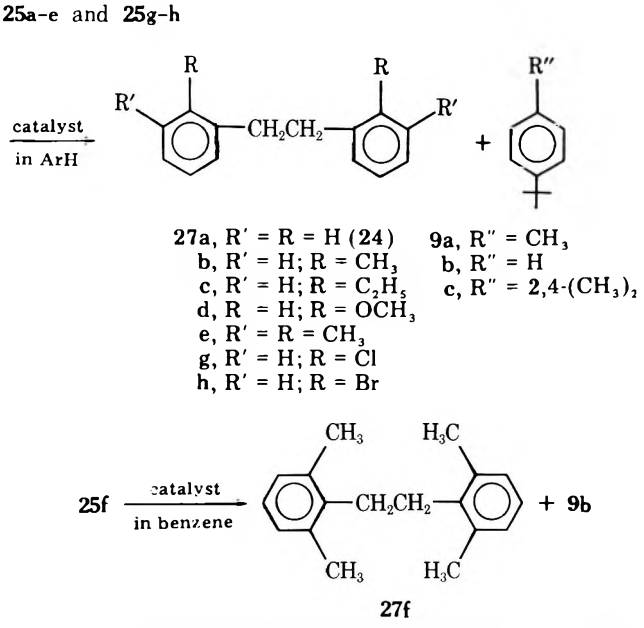
Run	Substrate	Catalyst[b]	Solvent	Time, h	Product (%)[c]
1[d]	**25a**	A	Toluene	3	**24** (84),[g] **9a** (90)
2[e]	**25a**	B	Toluene	6	**24** (80),[g] **9a** (95)
3[f]	**25a**	C	Toluene	0.5	**28** (12), **12c** (31), **24a** (5), **9a** (52)
4	**25b**	A	Benzene	2	**27b** (90),[g] **9b** (100)
5	**25c**	B	Benzene	8	**27b** (1[illegible]), **9b** (35)
6	**25d**	A	Benzene	5	**27c** (70),[g] **9b** (80)
7	**25d**	A	Benzene	6	**27d** (63),[g] **9b** (88)
8	**25d**	B	Benzene	9	No reaction
9	**25e**	A	Benzene	1	**27e** (9[illegible]),[g] **9b** (100)
10	**25e**	B	Benzene	3	**27e** (100),[g] **9b** (100)
11	**25f**	A	Benzene	1	**27f** (95),[g] **9b** (100)
12	**25f**	B	Benzene	3	**27f** (96),[g] **9b** (100)
13	**25g**	A	Benzene	5	No reaction
14	**25g**	C	Benzene	0.25	**27g** (97),[g] **9b** (100)

[a] Reaction temperature, 50 °C; catalyst/**25**, 0.2 mol/l mol. [b] A, $AlCl_3$–CH_3NO_2; B, $TiCl_4$; C, $AlCl_3$. [c] The yields were determined by gas chromatographic analyses unless otherwise indicated. [d] **25a** was recovered in [illegible]6% yield. [e] **25a** was recovered in 20% yield. [f] The large amount of resinous materials and unidentified compounds were formed. [g] The yields isolated are shown.

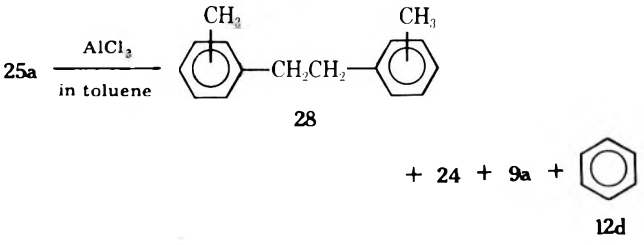
Scheme VI



Scheme VII



The $TiCl_4$ catalyzed transalkylation of **25b** gave also **27b** and **9b** in low yields, but the catalyst was not active for the transalkylation of **2c**.

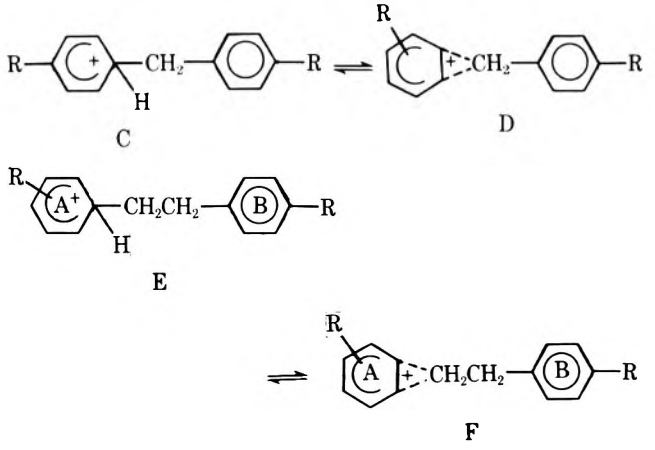


The $AlCl_3$–CH_3NO_2 catalyzed reactions of **25c, 25d, 25e,** and **25f** as well as **25a** and **25b** afforded the expected products **27c, 27d, 27e,** and **27f,** respectively.

However, in the case of **25d,** a large amount of the catalyst had to be used in order to obtain **27d** in good yield. The catalyst might react with the methoxy group of **25d** and **27d** to form a complex which reduce the catalytic activity and the basicity of **25d.** No observation of the $TiCl_4$ catalyzed transalkylation of **25d** might be explained for the same reason, since the $TiCl_4$ seems to be a weaker catalyst than $AlCl_3$–CH_3NO_2.

It should be noted that although $TiCl_4$ catalyzed the transalkylation of **2d** as mentioned above, the same reaction of **25f** gave only trans-*tert*-butylated product **27f.** In addition, the $AlCl_3$–CH_3NO_2 catalyzed transalkylation of **25f** gave also **27f** without the formation of any amount of the transaralkylated product. The above results might support, although not directly, the previous proposed mechanisms[9] of the transbenzylation of 4,4′-dihydroxydiphenylmethanes; that is, the intermediate D would be more important than the intermediate C for the occurrence of transbenzylation reaction.

However, even in the electron-rich diphenylethanes such as **27e** and **27f,** the substituent R on the ring B could not stabilize the σ-complex E and even π-complex **F,** in which the screen effect of the methylene group might take a negative role for the stabilization in contrast to D.



The $AlCl_3$–CH_3NO_2 catalyzed transalkylation of the electron-poor diphenylethane such as **25g** and **25h** did not afford any product, but the starting materials were recovered in almost quantitative yields. However, the $AlCl_3$ catalyzed transalkylation of **25g** afforded **27g** in good yield. In contrast to the case of **25g,** the $AlCl_3$ catalyzed transalkylation of **25h** gave only a small amount of **27h,** which could be detected by GC analyses but not isolated.

Based on the results obtained in the present study it could be concluded that: (i) the $AlCl_3$–CH_3NO_2 catalyzed transbenzylation of the electron-rich diphenylmethanes such as **2b–f** was observed; (ii) the transbenzylation of the electron-rich *tert*-butyldiphenylmethane having highly steric hindrance was easily catalyzed by even a weak catalyst like $TiCl_4$ without the trans-*tert*-butylation but not by $SnCl_4$; (iii) the $AlCl_3$–CH_3NO_2 catalyzed transalkylation of the electron-rich diphenylmethanes in benzene solution afforded only the first-step transbenzylated compound as a main product; (iv) however, when toluene and *m*-xylene were used as a solvent and acceptor in the transbenzylation of the electron-rich diphenylmethanes, the completely transbenzylated product was formed; (v) the $AlCl_3$–CH_3NO_2 catalyzed transbenzylation of the electron-poor diphenylmethanes was not observed; (vi) the alkyl, methoxy, and chloro substituted diphenylethanes such as **27b–g** could be prepared by using the *tert*-butyl group as a positional protective group; (vii) in contrast to diphenylmethanes, even the electron-rich diphenylethanes did not afford any transaralkylated product under the influence of $AlCl_3$–CH_3NO_2 catalyst; (viii) *tert*-butyldiphenylethanes seem to be higher basic compounds than *tert*-butyldiphenylmethanes, so that the former might be easily protonated by the weak Lewis acid such as $TiCl_4$ catalyst to afford the trans-*tert*-butylated product.

Experimental Section

All melting and boiling points are uncorrected. Mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet (isomerization energy 70 eV). NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer with Me_4Si and internal references and IR spectra were measured as KBr pellets or liquid film on NaCl plates on a Nippon Bunko IR-S spectrometer.

Analytical Procedure. The analyses were carried out by gas chromatography using a Yanagimoto gas chromatograph, Yanaco YR-101; 30% high vacuum silicon grease, 2 m, increase rate of column temperature, 15 °C/min; carrier gas, helium, 50 mL/min.

Preparation of 4,4′-Di-*tert*-butyldiphenylmethane (2a). To a solution of 120 g (542 mmol) of 2,6-di-*tert*-butyl-4-methylphenol and 70 g (417 mmol) of diphenylmethane (1) in 200 mL of nitromethane was added at 15 °C $AlCl_3$–CH_3NO_2 catalyst [$AlCl_3$ (107.3 g, 813 mmol)/nitromethane (200 mL)] over a period of 5 min. After the reaction mixture was stirred for 20 min more, it was poured into a large amount of ice–water. The organic layer was extracted with benzene and the benzene solution was dried over sodium sulfate and evaporated in vacuo to leave the residue which was washed with 10% NaOH aqueous solution affording 96.6 g (82.7%) of **2a:** colorless needles (from EtOH); mp 70–71 °C; NMR (CCl_4) δ 1.31 [18 H, s, $-C(CH_3)_3$], 7.38 (8 H, s, aromatic protons); IR (KBr) 2960, 1510, 1360, 1270, 1110, 1025, 865, 820 cm^{-1}. Anal. Calcd for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 90.03; H, 101.4. The washed 10% sodium hydroxide solution was acidified with 10% hydrochloric acid to give 56.3 g (96.2%) of *p*-cresol.

Chloromethylation of 2a. To a solution of 35 g (125 mmol) of **2a** and 80.5 g (100 mmol) of $ClCH_2OCH_3$ in 150 mL of CS_2 was added at −5 °C 20 mL (150 mmol) of $TiCl_4$. After the reaction mixture was stirred at −5 °C for 1 h, it was poured into 300 mL of ice–water. The organic layer was extracted with benzene. The benzene extract was dried over sodium sulfate and evaporated in vacuo to afford 36 g (76.4%) of 2,2′-dichloromethyl-4,4′-di-*tert*-butyldiphenylmethane (**3**): colorless plates (EtOH); mp 90–91 °C; NMR ($CDCl_3$) δ 1.30 [18 H, s, $-C(CH_3)_3$], 4.18 (2 H, s, $-CH_2-$), 4.50 (4 H, s, $-CH_2Cl$), 6.78–7.30 (6 H, m, aromatic protons); IR (KBr) 2960, 1500, 1260, 1200, 342, 740 cm^{-1}. Anal. Calcd for $C_{23}H_{30}Cl_2$: C, 73.20; H, 8.02. Found: C, 73.58; H, 8.03.

Preparation of 2b. According to Johnson's method,[11] a $LiAlH_4$–LiH reductive agent was prepared from 0.987 g of $LiAlH_4$ and 2.39 g of LiH in 500 mL of THF. To the agent was added a solution of 37.7 g (100 mmol) of **3** in 20 mL of THF under gently refluxing conditions over a period of 40 min. After the reaction mixture was refluxed for an additional 1 h, it was quenched with 25 mL of a mixture of water and THF (60:40 volume) at below 20 °C. The mixture was poured into a large amount of ice–water containing 20 mL of concentrated H_2SO_4 with stirring and was extracted with ether. The ether solution was dried over sodium sulfate and evaporated in vacuo to give 24.9 g (81%) of 4,4′-di-*tert*-butyl-2,2′-dimethyldiphenylmethane (**2b**): colorless plates (EtOH); mp 51–52 °C; NMR ($CDCl_3$) δ 1.30 [18 H, s, $-C(CH_3)_3$], 2.27 (6 H, s, $-CH_3$), 3.84 (2 H, s, $-CH_2-$), 6.70–7.30 (6 H, m, aromatic protons); IR (KBr) 2960, 1500, 1430, 1280, 850, 820 cm^{-1}. Anal. Calcd for $C_{23}H_{32}$: C, 89.55; H, 10.45. Found: C, 89.33; H, 10.43.

Preparation of 2c. To a solution of 4.95 g (25 mmol) of **5a** and 3.7 g (25 mmol) of **4a**[10] in 40 mL of CS_2 was gradually added 2 mL of $TiCl_4$ at 5 °C. After the reaction mixture was stirred at 5 °C for 90 min, it was treated and worked up as described above to afford 7.7 g (86.2%) of 5,5′-di-*tert*-butyl-2,2′-dimethyldiphenylmethane (**2c**): colorless liquid; bp 162–163 °C (3 mm); NMR (CCl_4) δ 1.20 [18 H, s, $-C(CH_3)_3$], 2.18 (6 H, s, $-CH_3$), 3.80 (2 H, s, $-CH_2-$), 6.80–6.96 (6 H, m, aromatic protons). Anal. Calcd for $C_{33}H_{32}$: C, 89.55; H, 10.45. Found: C, 89.59; H, 10.39.

Preparation of 2d. To a solution of 21.05 g (100 mmol) of **5b** and 16.23 g (100 mmol) of **4b**[10] in 100 mL of CS_2 was added 4 mL of $TiCl_4$ at 5 °C. After the reaction mixture was stirred for an additional 2 h, it was treated and worked up as described above to give 28 g (88.3%) of **2d:** colorless needles (EtOH); mp 135–136 °C; NMR ($CDCl_3$) δ 1.30 [18 H, s, $-C(CH_3)_3$], 2.14 (12 H, s, $-CH_3$), 4.02 (2 H, s, $-CH_2-$), 1.98 (4 H, s, aromatic protons). Anal. Calcd for $C_{25}H_{36}$: C, 89.22; H, 10.78. Found: C, 89.18; H, 10.71.

Preparation of 2e. To a solution of 21.5 g (100 mmol) of **5b** and 16.23 g (100 mmol) of **4c**[10] in 100 mL of CS_2 was added 4 mL of $TiCl_4$. After the reaction mixture was stirred for 3 h, it was treated and worked up as described above to afford 31.6 g (94%) of 4,5′-di-*tert*-butyl-2,2′,3′,6-tetramethyldiphenylmethane (**2e**): colorless needles (EtOH); mp 122–123 °C; IR (KBr) 2960, 1550, 1460, 1360, 870 cm^{-1}; NMR ($CDCl_3$) δ 1.09 [9 H, s, $-C(CH_3)_3$], 2.18 (6 H, s, $-CH_3$), 2.28 (3 H, s, $-CH_3$), 2.32 (3 H, s, $-CH_3$), 3.89 (2 H, s, $-CH_2-$), 6.37 (1 H, s), 7.00 (1 H, s) and 7.09 (2 H, s, aromatic protons). Anal. Calcd for $C_{25}H_{36}$: C, 89.22; H, 10.78. Found: C, 89.13; H, 10.76.

Preparation of 2f. A solution of 21.05 g (100 mmol) of **5c** and 16.23 g (100 mmol) of **4c** in 100 mL of CS_2 was treated and worked up as

described above to afford 26.88 g (90%) of **2f**: colorless needles (EtOH); mp 86.5–87.5 °C; IR (KBr) 2960, 1480, 1440, 1360, 880, 870, 725 cm^{-1}; NMR ($CDCl_3$) δ 1.18 [18 H, s, $-C(CH_3)_3$], 2.13 (6 H, s, $-CH_3$), 2.30 (6 H, s, $-CH_3$), 3.93 (2 H, s, $-CH_2-$), 6.77–7.10 (4 H, m, aromatic protons). Anal. Calcd for $C_{25}H_{36}$: C, 89.22; H, 10.78. Found: C, 89.03; H, 10.88.

Preparation of 2g. To a solution of 32.4 g (200 mmol) of **4b** and 37.95 g (300 mmol) of benzyl chloride (**7a**) in 100 mL of CS_2 was added at 5 °C 8 mL (40 mmol) of $TiCl_4$. After the reaction mixture was stirred at 5 °C for 4 h, it was treated and worked up as described above to afford 33.72 g (69%) of 4-*tert*-butyl-2,6-dimethyldiphenylmethane (**2g**): colorless needles (EtOH); mp 43–45 °C; bp 132–134 °C (3 mmHg); IR (KBr) 2660, 1600, 1490, 1450, 1200, 1040, 880, 715, 700 cm^{-1}; NMR ($CDCl_4$) δ 1.30 [9 H, s, $-C(CH_3)_3$], 2.20 (6 H, s, $-CH_2-$), 6.82–7.20 (7 H, m, aromatic protons). Anal. Calcd for $C_{19}H_{24}$: C, 90.24; H, 9.58. Found: C, 90.34; H, 9.53.

Preparation of 5a. To a solution of 100 g (676 mmol) of **4a** and 136 g (1.7 mmol) of $ClCH_2OCH_3$ in 200 mL of CS_2 was added at 5 °C 23 mL (140 mmol) of $TiCl_4$. After the reaction mixture was stirred for 90 min, it was poured into 300 mL of ice–water and extracted with ether. The ether extract was dried over sodium sulfate and evaporated in vacuo to leave a residue which was distilled under reduced pressure to afford 9.1 g (9.1%) of **4a** and 95.5 g (71.1%) of **5a**: colorless liquid; bp 94–95 °C (3 mm); IR (NaCl) 2970, 1500, 1360, 1250, 825, 740 cm^{-1}; NMR (CCl_4) δ 1.30 [9 H, s, $-C(CH_3)_3$], 2.35 (3 H, s, $-CH_3$), 4.55 (2 H, s, $-CH_2-$), 7.00–7.31 (3 H, m, aromatic protons).

Preparation of 5b. To a solution of 50 g (308 mmol) of **4b** and 49.6 g (616 mmol) of $ClCH_2OCH_3$ in 150 mL of CS_2 was added at 5 °C 14 mL (70 mmol) of $TiCl_4$. The reaction mixture was stirred at 5 °C for 1 h and treated as described above to afford 60.54 g (93.3%) of 4-*tert*-butyl-2,6-dimethylbenzyl chloride (**5b**) with 2.15 g (4.1%) of **2d**. **5b**: colorless liquid; bp 95–96 °C (3 mm) [lit.[13] bp 135–136 °C (10 mm)]; IR (KBr) 2960, 1460, 1260, 870, 750, 680 cm^{-1}; NMR ($CDCl_3$) δ 1.30 [9 H, s, $-C(CH_3)_3$], 2.41 (6 H, s, $-CH_3$), 4.62 (2 H, s, $-CH_2-$), 7.07 (2 H, s, aromatic protons).

Preparation of 5c. A mixture of 50 g (308 mmol) of **4c** and 49.6 g (616 mmol) of chloromethyl ether was treated with 14 mL (70 mmol) of $TiCl_4$ and worked up as described above to afford 50 g (77.1%) of 5-*tert*-butyl-2,3-dimethylbenzyl chloride (**5c**) and 8.28 g (16%) of **2f**. **5c**: colorless needles; mp 45–47 °C (lit.[13] mp 48.5–49.0 °C); bp 117–118 °C (3 mm); IR (KBr) 2960, 1480, 1460, 1350, 1260, 880, 740, 690 cm^{-1}; NMR ($CDCl_4$) δ 1.30 [9 H, s, $-C(CH_3)_3$], 2.27 (6 H, s, $-CH_3$), 4.58 (2 H, s, $-CH_2-$), 7.16 (2 H, s, aromatic protons).

Preparation of 5d. To a solution of 100 g (0.616 mol) of 4-*tert*-butylethylbenzene[10] and 99.2 g (1.23 mol) of $ClCH_2OCH_3$ in 300 mL of CS_2 was added at 5 °C 28 mL (0.14 mol) of $TiCl_4$. After the reaction mixture was stirred for 2 h, it was poured into 500 mL of ice–water and extracted with ether. The ether solution was dried over sodium sulfate and evaporated to leave the residue, which was distilled under reduced pressure to afford 80.94 g (62.4%) of 5-*tert*-butyl-2-ethylbenzyl chloride (**5d**) and 27.13 g of the starting compound [bp 57–58 °C (3 mm)]. **5d**: colorless liquid; bp 102–102 °C (3 mm); NMR (CCl_4) δ 1.30 [9 H, s, $-C(CH_3)_3$ and 3 H, t, $-CH_3$], 2.70 (2 H, q, $-CH_2-$), 4.51 (2 H, s, $-CH_2CH_2-$), 7.10–7.30 (3 H, m, aromatic protons).

Preparation of 5e. After a mixture of 109.3 g (0.674 mol) of 4-*tert*-butylanisole,[10] 10 g (0.33 mol) of paraformaldehyde, and 104 g of 31% hydrochloric acid was stirred vigorously at 55 °C for 7 h, it was cooled to room temperature and extracted with benzene. The benzene solution was washed with 10% sodium carbonate solution, dried over sodium sulfate, and evaporated in vacuo to leave the residue, which was distilled under reduced pressure to afford 39.9 g (28.1%) of 5-*tert*-butyl-2-methoxybenzyl chloride (**5e**) and 60 g of the starting compound [bp 73–74 °C (3 mm)]. **5e**: colorless liquid; bp 117–118 °C (3 mm); NMR (CCl_4) δ 1.26 [9 H, s, $-C(CH_3)$], 3.72 (3 H, s, $-CH_3$), 4.51 (2 H, s, $-CH_2-$), 6.59–7.25 (3 H, m, aromatic protons). When the $TiCl_4$ catalyzed chloromethylation of 4-*tert*-butylanisole with $ClCH_2OCH_3$ was carried out, **5e** was not obtained but only large amount of resinous material was formed.

Preparation of 5f. To a solution of 51.9 g (0.308 mol) of 4-*tert*-butylchlorobenzene[14] and 49.6 g (0.616 mol) of $ClCH_2OCH_3$ in 75 mL of CS_2 was added at 5 °C 14 mL of $TiCl_4$. After the reaction mixture was stirred for 10 h, it was treated and worked up as described above to afford 31.4 g (47.0%) of 5-*tert*-butyl-2-chlorobenzyl chloride (**5f**) and 22.43 g of the starting compound [bp 58 °C (3 mm)]. **5f**: colorless liquid; bp 105–107 °C (3 mm); NMR (CCl_4) δ 1.30 [18 H, s, $-C(CH_3)_3$], 4.95 (2 H, s, $-CH_2-$), 7.10–7.45 (3 H, m, aromatic protons).

Preparation of 5g. Similarly a solution of 131.2 g (0.616 mol) of 4-*tert*-butylbromobenzene,[14] 99.2 g (1.23 mol) of $ClCH_2OCH_3$, and 28 mL of $TiCl_4$ in 150 mL of CS_2 was treated and worked up as described above to afford 70.3 g (52.7%) of 5-*tert*-butyl-2-bromobenzyl chloride (**5g**) and 44.3 g of the starting compound. **5g**: colorless liquid; bp 130–132 °C (5 mm); NMR (CCl_4) δ 1.30 [18 H, s, $-C(CH_3)_3$], 4.60 (2 H, s, $-CH_2-$), 7.27–7.54 (3 H, m, aromatic protons).

The $TiCl_4$ Catalyzed Benzylation of Benzene with 5b. To a solution of 21.04 g (0.1 mol) of **5b** in 120 mL of benzene 4 mL of $TiCl_4$ was gradually added at room temperature. After the reaction mixture was stirred for 1 h, it was treated and worked up as described above to afford 10 g (50%) of **6** and 11 g (43%) of **2g**.

Preparation of 6. To a solution of 16.2 g (100 mmol) of **4b** and 8.75 g (50 mmol) of 1,4-bis(chloromethyl)benzene (**8**) in 5 mL of CS_2 was added 4 mL (10 mmol) of $TiCl_4$ at 5 °C. After the reaction mixture was stirred for 3 h, it was treated and worked up as described above to afford 12 g (59.1%) of 1,4-bis(4-*tert*-butyl-2,6-dimethylbenzyl)-benzene (**6**): colorless prisms (EtOH); mp 196–198 °C; IR (KBr) 2960, 1485, 1450, 1360, 880 cm^{-1}; NMR ($CDCl_3$) δ 1.30 [18 H, s, $-C(CH_3)_3$], 2.20 (12 H, s, $-CH_3$), 3.94 (4 H, s, $-CH_2-$), 6.88–7.08 (8 H, m, aromatic protons). Anal. Calcd for $C_{32}H_{42}$: C, 90.08; H, 9.92. Found: C, 89.52; H, 9.86.

Preparation of 14b. To a solution of 14.5 g (0.1 mol) of CS_2 was added 8 mL of $TiCl_4$ at 5 °C. After the reaction mixture was stirred at 5 °C for 2 h, it was treated and worked up as described above to give 13.28 g (53%) of **14b**: colorless liquid; bp 139–142 °C (3 mm); IR (NaCl) 2960, 1460, 1360, 820, 740 cm^{-1}; NMR (CCl_4) δ 1.20 [9 H, s, $-C(CH_3)_3$], 2.14 (3 H, s, $-CH_3$), 2.22 (3 H, s, $-CH_3$), 3.80 (2 H, s, $-CH_2-$), 6.60–7.10 (7 H, m, aromatic protons). Anal. Calcd for $C_{19}H_{24}$: C, 90.24; H, 9.58. Found: C, 89.98; H, 9.59.

Preparation of 21. A solution of 32.4 g (200 mmol) of **4c** and 37.95 g (300 mmol) of **7a** in 100 mL of CS_2 was treated and worked up as described above to afford 24.36 g (48.2%) of **21** with 10 g of starting compound **4c**. **21**: colorless liquid; bp 137–139 °C (3 mm); IR (NaCl) 2960, 1600, 1500, 1450, 1360, 880, 735, 700 cm^{-1}; NMR (CCl_4) δ 1.27 [9 H, s, $-C(CH_3)_3$], 2.00 (3 H, s, $-CH_3$), 3.90 (2 H, s, $-CH_2-$), 6.70–7.20 (7 H, m, aromatic protons); mass spectrum *m/e* 252 (M^+). Anal. Calcd for $C_{19}H_{24}$: C, 90.24; H, 9.58. Found: C, 90.50; H, 9.45.

General Procedure of the Transalkylation of 2. After a mixture of 30 equiv of benzene (or toluene, *m*-xylene), 0.2 equiv of the catalyst/equiv of **2**, and 1 mol of **2** had been maintained at a desired, constant temperature and a specified reaction time with stirring, the reaction mixture was separated and dried over sodium sulfate. A definite amount of the benzene solution was analyzed by gas chromatography. After the analyses, the products were isolated and purified by distillation and/or recrystallization, respectively. The reaction conditions and the yields are summarized in Table I.

11: colorless liquid; bp 110–112 °C (3 mm); IR (NaCl) 3020, 2960, 1600, 1055, 740 cm^{-1}; NMR (CCl_4) δ 2.18 (6 H, s, $-CH_3$), 3.78 (2 H, s, $-CH_2-$), 6.70–7.20 (8 H, m, aromatic protons). Anal. Calcd for $C_{15}H_{16}$: C, 91.79; H, 8.22. Found: C, 91.33; H, 8.29. **16**: colorless liquid: bp 107–109 °C (3 mm); IR (NaCl) 3040, 3970, 2940, 1600, 1450, 735, 700 cm^{-1}; NMR (CCl_4) δ 2.10 (3 H, s, $-CH_3$), 2.23 (3 H, s, $-CH_3$), 3.83 (2 H, s, $-CH_2-$), 6.85–7.20 (8 H, m, aromatic protons). Anal. Calcd for $C_{15}H_{16}$: C, 91.79; H, 8.22. Found: C, 91.76; H, 8.16.

22: colorless liquid; bp 123 °C (33 mm); IR (NaCl) 3070, 3040, 2920, 1600, 1500, 1450, 790, 730, 700 cm^{-1}; NMR (CCl_4) δ 2.13 (6 H, s, $-CH_3$), 3.79 (2 H, s, $-CH_2$), 6.30–7.20 (8 H, m, aromatic protons). Anal. Calcd for $C_{15}H_{16}$: C, 91.79; H, 8.22. Found: C, 91.74; H, 8.19.

23: colorless liquid; IR (NaCl) 2960, 1480, 1360, 860, 750 cm^{-1}; mass spectrum *m/e* 280 (M^+); NMR (CCl_4) δ 1.10 [9 H, s, $-C(CH_3)$], 1.98 (3 H, s, $-CH_3$), 2.10 (3 H, s, $-CH_3$), 2.22 (6 H, s, $-CH_3$). This compound **23** was separated by using separative gas chromatography.

Preparation of 25a. To a solution of 54.8 g (0.3 mol) of diphenylethane (**24**) and 86 g (0.39 mol) of 2,6-di-*tert*-butyl-*p*-cresol in 120 mL of nitromethane was added at 15 °C a $AlCl_3$–CH_3NO_2 solution [67 g (0.507 mol) of $AlCl_3$/120 mL of CH_3NO_2]. After the reaction mixture was stirred for 5 min, it was poured into a large amount of ice–water and the organic layer was extracted with benzene. The benzene solution was dried over sodium sulfate and evaporated in vacuo to leave the residue in which benzene was added again. The benzene solution was extracted with 10% sodium hydroxide. The benzene was washed with water, dried over sodium sulfate, and evaporated in vacuo to afford 79 g (90%) of **25a**: colorless plates (EtOH); mp 154–155 °C; NMR (CCl_4) δ 1.30 [18 H, s, $-C(CH_3)_3$], 2.83 (4 H, s, $-CH_2CH_2-$), 6.95–7.30 (8 H, aromatic protons). Anal. Calcd for $C_{22}H_{30}$: C, 88.73; H, 10.27. Found: C, 89.48; H, 10.27. *p*-Cresol was obtained almost quantitatively from the 10% sodium hydroxide extract by acidification with 10% hydrochloric acid.

Preparation of 25b. To a solution of CH_3MgI (prepared from 150 g of methyl iodine and 25 g of magnesium) in 400 mL of ether was gradually added a solution of **5a** in 1 h under the condition of reflux. After the reaction mixture was refluxed for an additional 2 h, it was quenched with 10% hydrochloric acid and extracted with ether. The

ether extract was dried over sodium sulfate and evaporated in vacuo to leave the residue, in which a small amount of ethanol was added to afford 45 g (72%) of 5,5′-di-*tert*-butyl-2,2′-dimethyldiphenylethane (**25b**) as a colorless crystal, and the filtrate afforded 9.1 g (13.4%) of 4-*tert*-butyl-2-ethyltoluene (**26b**). **25b:** colorless needles (EtOH); mp 55–56 °C; NMR (CCl_4) δ 1.25 [18 H, s, $-C(CH_3)_3$], 2.15 (6 H, s, $-CH_3$), 2.81 (4 H, s, $-CH_2CH_2-$), 6.96 (6 H, s, aromatic protons). Anal. Calcd for $C_{24}H_{34}$: C, 89.39; H, 10.62. Found: C, 89.35; H, 10.66. **26b:** colorless liquid; bp 69–71 °C (3 mm).

Preparation of 25c. To a solution of methylmagnesium iodide (from 60 g of methyl iodide and 10 g of magnesium) in 150 mL of ether was added a solution of 32.7 g (0.155 mol) of **5d** in 50 mL of ether. The reaction mixture was treated and worked up as described above to afford 23.4 g (86.5%) of 5,5′-di-*tert*-butyl-2,2′-diethyldiphenylethane (**25c**) and 4.2 g (16.6%) of 2-ethyl-4-*tert*-butylethylbenzene (**26c**). **25c:** colorless liquid; bp 79–82 °C (3 mm); NMR (CCl_4) δ 1.22 (6 H, t, $-CH_3$), 1.25 [18 H, s, $-C(CH_3)_3$], 2.56 (4 H, q, $-CH_2CH_2-$), 7.03 (6 H, s, aromatic protons). Anal. Calcd for $C_{26}H_{38}$: C, 89.08; H, 10.92. Found: C, 88.78; H, 10.94. **26c:** colorless liquid; bp 78–82 °C (3 mm).

Preparation of 25d. An ether solution of methylmagnesium iodide (CH_3I, 60 g; Mg, 10 g) was treated with a solution of 32.7 g (0.155 mol) of **5e** in 50 mL of ether and the reaction mixture was worked up as described above to afford 17 g (62.6%) of 5,5′-di-*tert*-butyl-2,2′-dimethoxydiphenylethane (**25d**) and 6 g (20.3%) of 4-*tert*-butyl-2-ethylanisole (**26d**). **25d:** colorless needles (EtOH); mp 92–93 °C; NMR ($CDCl_4$) δ 1.20 [18 H, s, $-C(CH_3)_3$], 2.82 (4 H, s, $-CH_2CH_2-$), 3.71 (6 H, s, $-CH_3$), 6.54–7.12 (6 H, m, aromatic protons). Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.05; H, 9.71. **26d:** colorless liquid; bp 83–85 °C (3 mm).

Preparation of 25e. Similarly 32.7 g (0.155 mol) of **5c** was treated with methylmagnesium iodide (CH_3I, 60 g; Mg, 10 g) in the same manner as described above to afford 20.4 g (75.2%) of 5,5′-di-*tert*-butyl-2,2′,3,3′-tetramethyldiphenylethane (**25e**): colorless needles (EtOH); mp 87–88 °C; NMR (CCl_4) δ 1.23 [18 H, s, $-C(CH_3)_3$], 2.08 (6 H, s, $-CH_3$), 2.21 (6 H, s, $-CH_3$), 2.80 (4 H, s, $-CH_2-$), 6.80–7.00 (4 H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}$: C, 89.08; H, 10.92. Found: C, 89.03; H, 10.88.

Preparation of 25f. Similarly 24.1 g (89.8%) of 4,4′-di-*tert*-butyl-2,2′,6,6′-tetramethyldiphenylethane (**25f**) and 3.07 g (10.5%) of 4-*tert*-butyl-2,6-dimethylethylbenzene (**26f**) were obtained from 32.7 g (0.155 mol) of **5b** in same manner as described above. **25f:** colorless needles (EtOH); mp 220–221 °C (lit.[13] mp 216–217 °C); NMR (CCl_4) δ 1.30 [18 H, s, $-C(CH_3)_3$], 2.42 (12 H, s, $-CH_3$), 2.78 (4 H, s, $-CH_2-$), 7.05 (4 H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}$: C, 89.08; H, 10.92. Found: C, 88.99; H, 10.86. **26f:** colorless liquid.

Preparation of 25g. To a solution of methylmagnesium iodide (30 g of CH_3I, 5 g of Mg) in 75 mL of ether was added a solution of 16.82 g (77.5 mmol) of **5f** in 25 mL of ether. After the reaction mixture was refluxed for 3 h, it was treated and worked up as described above to afford 9.5 g (70%) of 5,5′-di-*tert*-butyl-2,2′-dichlorodiphenylethane (**25g**): colorless needles (EtOH); mp 113–114 °C; NMR (CCl_4) δ 1.30 [18 H, s, $-C(CH_3)_3$], 2.94 (4 H, s, $-CH_2-$), 7.10–7.30 (6 H, m, aromatic protons). Anal. Calcd for $C_{22}H_{28}Cl_2$: C, 72.72; H, 7.77. Found: C, 72.43; H, 7.75.

Preparation of 25h. To a solution of methylmagnesium iodide (30 g of CH_3I, 5 g of Mg) in 75 mL of ether was added a solution of 20.3 g (77.5 mmol) of **5g** in 25 mL of ether over a period of 30 min. The reaction mixture was refluxed for 3 h and was treated and worked up as described above to afford 12.5 g (71.3%) of 5,5′-di-*tert*-butyl-2,2′-dibromodiphenylethane (**25h**): colorless needles (EtOH); mp 92–93 °C; NMR (CCl_4) δ 1.30 [18 H, s, $-C(CH_3)_3$], 2.95 (4 H, s, $-CH_2-$), 7.15–7.50 (6 H, m, aromatic protons). Anal. Calcd for $C_{22}H_{28}Br_2$: C, 58.42; H, 6.24. Found: C, 58.31; H, 6.20.

The Transalkylation of 25. After a mixture of 30 equiv of benzene (or toluene, *m*-xylene), 0.2 equiv of the catalyst/equiv of **25**, and 1 mol of **25** had been maintained at a desired, constant temperature and a specified reaction time with stirring, the reaction mixture was quenched with 10% hydrochloric acid. The layer was separated and dried over sodium sulfate. A definite amount of benzene solution was analyzed by gas chromatography. After the analyses, the products were isolated and purified by distillation and/or recrystallization, respectively. The reaction conditions and the yields are summarized in Table III.

27b: colorless needles (EtOH); mp 65–66 °C; NMR (CCl_4) δ 2.23 (6 H, s, $-CH_3$), 2.79 (4 H, s, $-CH_2CH_2-$), 7.02 (8 H, s, aromatic protons). Anal. Calcd for $C_{16}H_{18}$: C, 91.04; H, 8.63. Found: C, 91.23; H, 8.62.

27c: colorless plates (EtOH); mp 26–28 °C; NMR (CCl_4) δ 1.20 (6 H, t, $-CH_3$), 2.63 (4 H, q, $-CH_2-$), 2.85 (4 H, s, $-CH_2CH_2-$), 7.18 (8 H, s, aromatic protons). Anal. Calcd for $C_{18}H_{22}$: C, 90.07; H, 9.30. Found: C, 90.67; H, 9.26.

27d: colorless needles (EtOH); mp 80–82 °C; NMR (CCl_4) δ 2.82 (4 H, s, $-CH_2CH_2-$), 3.77 (6 H, s, $-OCH_3$), 6.60–7.10 (6 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.30; H, 7.54.

27e: colorless needles (EtOH); mp 110–111 °C; NMR (CCl_4) δ 2.19 (6 H, s, $-CH_3$), 2.25 (6 H, s, $-CH_3$), 2.80 (4 H, s, $-CH_2-$), 6.92 (6 H, s, aromatic protons). Anal. Calcd for $C_{18}H_{22}$: C, 90.70; H, 9.30. Found: C, 89.02; H, 9.35.

27f: colorless needles (EtOH); mp 123–125 °C; NMR (CCl_4) δ 2.21 (12 H, s, $-CH_3$), 2.75 (4 H, s, $-CH_2-$), 6.87 (6 H, s, aromatic protons). Anal. Calcd for $C_{18}H_{22}$: C, 90.70; H, 9.30. Found: C, 90.33; H, 9.38.

27g: colorless needles; mp 57–58 °C; NMR (CCl_4) δ 3.00 (4 H, s, $-CH_2-$), 7.00–7.40 (8 H, m, aromatic protons). Anal. Calcd for $C_{14}H_{12}Cl_2$: C, 66.95; H, 4.82. Found: C, 66.89; H, 4.79.

Registry No.—**1**, 101-81-5; **2a**, 19099-48-0; **2b**, 65276-21-3; **2c**, 65276-22-4; **2d**, 65338-71-8; **2e**, 65276-23-5; **2f**, 65276-24-6; **2g**, 65276-25-7; **3**, 65276-26-8; **4a**, 98-51-1; **4b**, 98-19-1; **4c**, 7397-06-0; **5b**, 19387-83-8; **5c**, 28162-13-2; **5d**, 65276-27-9; **5e**, 22252-73-9; **5f**, 65276-28-0; **5g**, 65276-29-1; **6**, 65276-30-4; **7a**, 100-44-7; **7b**, 552-45-4; **8**, 623-25-6; **11**, 1634-74-8; **14b**, 65276-31-5; **16**, 28122-29-4; **21**, 65276-32-6; **22**, 62155-16-2; **23**, 65276-33-7; **24**, 103-29-7; **25a**, 22927-07-7; **25b**, 65276-09-7; **25c**, 65276-10-0; **25d**, 65276-11-1; **25e**, 65276-12-2; **25f**, 65276-13-3; **25g**, 62576-14-4; **25h**, 65276-15-5; **26b**, 65276-16-6; **26c**, 65276-17-7; **26d**, 65276-18-8; **26f**, 65276-19-9; **27b**, 952-80-7; **27c**, 27499-60-1; **27d**, 14310-34-0; **27e**, 65276-20-2; **27f**, 25115-79-1; **27g**, 6639-40-3; 2,6-di-*tert*-butyl-4-methylphenol, 128-37-0; $ClCH_2OCH_3$, 107-30-2; 4-*tert*-butylethylbenzene, 7364-19-4; 4-*tert*-butylanisole, 5396-38-3; hydrochloric acid, 7647-01-0; 4-*tert*-butylchlorobenzene, 3972-56-3; 4-*tert*-butylbromobenzene, 3972-65-4.

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Pyrolysis of Unsaturated Compounds. 2. Pyrolysis of Ketones[1,2]

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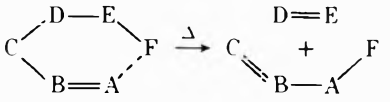
In order to compare the ease of pyrolysis of ketones with that of esters, a series of ketones was pyrolyzed in an apparatus commonly used for preparative ester pyrolysis. Thus, when heptane-2,6-dione was pyrolyzed at 650 °C, the major products of pyrolysis were methyl vinyl ketone (17%) and acetone (22%). Since 66% of the starting diketone was recovered unchanged, the yields of acetone and methyl vinyl ketone based on unrecovered material were 61 and 45%, respectively. In a similar experiment at 650 °C, pyrolysis of methyl neopentyl ketone gave a 17% yield of acetone and an 18% yield of isobutylene. Since 61% of the methyl neopentyl ketone was recovered unchanged, the yields of acetone and isobutylene, based on unrecovered material, were 44 and 46%, respectively. When methyl isobutyl ketone was pyrolyzed at 650 °C, 75% of the ketone was recovered unchanged and the major products were propylene (10%) and acetone (7%); however, at the same time an 8% yield of isobutylene was obtained. Pyrolysis of methyl *n*-propyl ketone at 650 °C gave an 87% recovery of the ketone plus a 6% yield of acetone and a 3% yield of ethylene, as well as a 5% yield of methyl vinyl ketone plus some propylene. Thus, it appears that a ketone is considerably more thermally stable than an ester, requiring some 150 °C higher temperature for a comparable extent of decomposition.

Since previous work in these laboratories had shown that pyrolysis of esters was a very excellent synthetic tool for the preparation of a wide variety of strained dienes,[4] isomers of aromatic compounds,[5] and highly reactive monomers,[6] we wanted to determine how general such a pyrolysis reaction was and what other unsaturated compounds might undergo a similar cyclic molecular decomposition. Thus we became interested in what other atoms could be located in the six-membered ring and still have the cyclic molecular mechanism operate.

In ester pyrolysis A and C are oxygen atoms while in the Chugaev reaction, which involves the pyrolysis of a xanthate



ester, a sulfur atom is located in position A. Similarly, previous work in these laboratories showed that pyrolysis of amides,[7,8] in which C is a nitrogen atom, occurs by the same cyclic mechanism but involves a temperature that is at least 60 °C higher than that required for ester pyrolysis. More recently, a study of the pyrolysis of vinyl ethers[1] in which A is a carbon atom showed that these materials pyrolyze at a temperature 40–50 °C lower than the temperature necessary for comparable ester pyrolysis. The ease of pyrolysis of various compounds can be rationalized by the assumption that the transition state in the cyclic mechanism looks more like the products than the starting materials, and that if a stable double bond between A and B is converted to a less stable double bond between C and B, a higher temperature is required for pyrolysis than is necessary for the pyrolysis of the symmetrical ester. Conversely, if a high-energy double bond between A and B is converted to a more stable double bond between C and B in the products, a temperature lower than that required for the pyrolysis of the symmetrical ester group is noted.

In such a system a ketone which has a carbon atom in position C and oxygen in position A is a counterpart to the vinyl ether which has the oxygen in position C and a carbon in position A. For this reason it was of interest to study the pyrolysis of ketones in order to see if the relationship discussed above is followed and that ketones do indeed pyrolyze by a cyclic six-membered mechanism and require temperatures considerably higher than those required for ester pyrolysis.

Although there are many examples in the literature of the photolysis of ketones,[9-12] little work has been done on the pyrolysis of ketones. Methyl *n*-propyl ketone is one ketone for which both photolysis and pyrolysis data are available. However, because of the lack of uniformity in pyrolysis and photolysis conditions, the results are hard to compare. McNesby and Gordon[13] reported that the pyrolysis and photolysis of 2-pentanone-1,1,1,3,3,-d_5 gave more acetone-d_6 than acetone-d_5. If the cyclic mechanism were operative, all the acetone should have been d_5. They concluded that in the pyrolysis region the reaction appeared to involve a free-radical mechanism. However, Ausloos and Murod[14] studied the photolysis of 2-pentanone-1,1,1,3,3-d_5 and reported that 90% of the acetone obtained was acetone-d_5. They concluded that the intermolecular cleavage through a six-membered ring was operating.

Guenther[15] reported the formation of large quantities of methyl vinyl ketone plus some acetone from the gas-phase thermal decomposition of methyl *n*-propyl ketone at 500–530 °C. Waring and Garik[16] pyrolyzed methyl *n*-propyl ketone and concluded that it decomposed predominately through a free-radical mechanism. Blades and Sandhu[17] reported that at 652 °C methyl *n*-propyl ketone undergoes almost no decomposition but produced minor amounts of methane, ethylene, and acetone. They also reported that the rate constant for acetone formation was 0.016 s^{-1} with an Arrhenius factor of 59. Furukawa and Naruchi[18] pyrolyzed methyl *n*-propyl ketone at 500 °C over calcium carbonate to yield acetone plus di-*n*-propyl ketone.

In 1957, Walters and Barry[19] studied the gas-phase thermal decomposition of methyl *n*-butyl ketone from 430 to 500 °C. The principal products of the reaction during early stages of the reaction are (1) propylene and acetone, (2) ethane and methyl vinyl ketone, and (3) methane, carbon monoxide, and 1-butene. Since methane and carbon monoxide grow in importance during the decomposition, they are probably formed by the decomposition of intermediate products. Waring et al.[20-22] studied the decomposition of acetone, methyl ethyl ketone, and diethyl ketone and concluded that all three decomposed primarily through a free-radical chain mechanism. Skraup and Guggenheim[23] reported that the products from heating dibenzoylpropane for 20 h at 330 °C in a bomb were acetophenone and phenyl vinyl ketone. Although the authors did not postulate a mechanism, the products can be rationalized on the basis of a cyclic mechanism. Finally, Allan, McGee, and Ritchie[24] studied the pyrolysis of acetylacetone at 500 °C and reported the production of acetone, ketene, and isopropenyl acetate, plus some methylacetylene, ethylene, and methane. Blades and Sandhu[17] also reported that acetylace-

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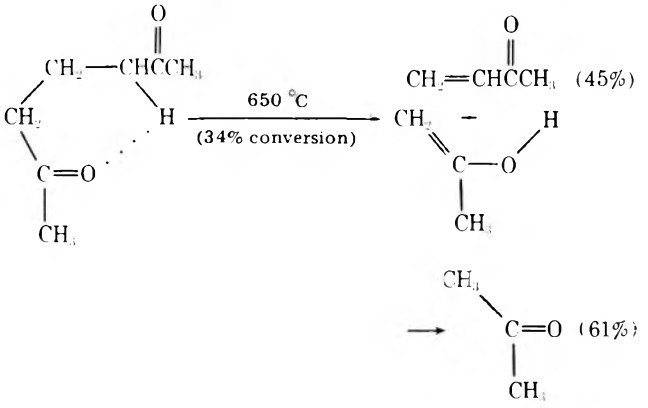
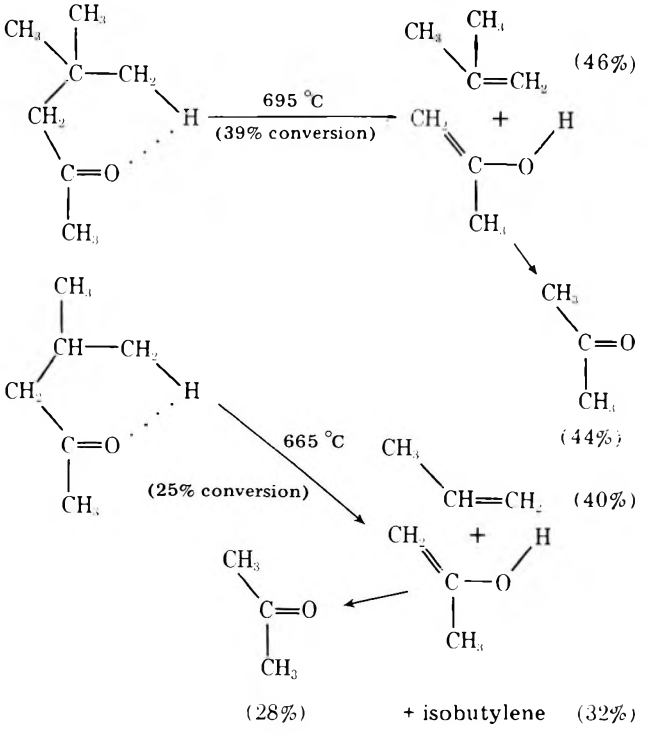
tone gave acetone when heated at 505 °C, but they did not detect the expected ketene. Thus, although there are fairly extensive data in the literature on the photolysis and pyrolysis of ketones, there has been no systematic study that would allow direct comparison with ester pyrolysis and apparently no attempt has been made to maximize the yield of products from the pyrolysis of ketones. We therefore undertook the study of several acyclic ketones by conducting the pyrolysis in the same apparatus and under conditions that were comparable to those used for the pyrolysis of esters.

Heptane-2,6-dione was selected for the initial studies since the compound was symmetrical and contained activated γ-hydrogen atoms. The procedure of Cope, Dryden, Overberger, and D'Addieco[25] was used to synthesize the heptane-2,6-dione dioxime and the method of Overberger et al.[26] was used to convert the dioxime to the dione in a 42% yield. Pyrolysis at 650 °C gave a 22% yield of acetone and a 17% yield of methyl vinyl ketone, together with a 66% recovery of the diketone. The yields of acetone and methyl vinyl ketone, based on unrecovered starting material, were 61 and 45%, respectively.

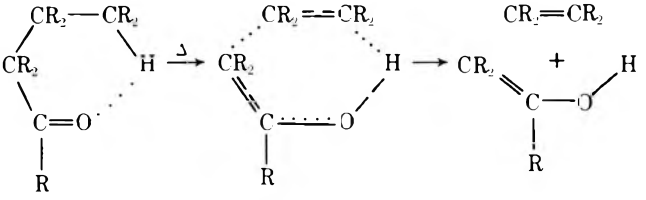


A modification of the procedure of Mosher and Cox[27] was used to prepare methyl neopentyl ketone by the oxidation of technical grade diisobutylene with potassium dichromate in an overall yield of 47%. Pyrolysis of the methyl neopentyl ketone at 690–695 °C gave a 17% yield of acetone and an 18% yield of isobutylene together with a 61% recovery of the starting ketone. The yields of acetone and isobutylene (based on unrecovered starting material) were, therefore, 44 and 46%, respectively. At 500 °C, a temperature at which *tert*-butyl acetate is essentially completely pyrolyzed to isobutylene and acetic acid, the methyl neopentyl ketone is recovered unchanged. In a very similar manner 4-methyl-2-pentanone was pyrolyzed at 665 °C to produce in the following yields: propylene (10%), acetone (7%), and recovery of the starting ketone (75%); in addition an 8% yield of isobutylene was obtained. The yields of acetone and propylene, based on unrecovered starting material, were 28 and 40%, respectively. The extent of decomposition appears to be somewhat less than in the case of the heptane-2,6-dione or the methyl neopentyl ketone.



Methyl *n*-propyl ketone proved to be more thermally stable than the more highly substituted ketones previously discussed. Pyrolysis of methyl *n*-propyl ketone at 650 °C gave an 87% recovery of starting material plus a 6% conversion to acetone and a 3% conversion to ethylene, both products expected from the operation of the cyclic mechanism. However, there also was obtained a 5% conversion to methyl vinyl ketone, the formation of which can be rationalized by the operation of a free-radical chain reaction involving the abstraction of the α-hydrogen atom. Finally, for comparison acetone was treated at 650 °C under the conditions used for the pyrolysis of methyl *n*-propyl ketone; the acetone was recovered unchanged and no indication of decomposition was noted.

Thus, it appears that ketones are considerably more thermally stable than esters, requiring some 150 °C higher temperature for a comparable extent of decomposition. This is in marked contrast to the vinyl ethers,[1] which require a temperature some 40–50 °C lower than that required for a comparable degree of pyrolysis of an ester. The data from the pyrolysis of the ketones support the concept that the transition state for the cyclic six-membered mechanism resembles the products more than it does the starting materials.



The process of changing from a relatively stable carbon–oxygen double bond in the starting ketone to the less stable, higher energy carbon-to-carbon double bond character in the transition state requires a higher temperature for operation. The introduction of a quaternary carbon in the starting ketone tends to promote the thermal decomposition in order to relieve some of the strain. Similarly, the introduction of a second carbonyl group, as in heptane-2,6-dione, not only activates the hydrogen atom by reducing its bond strength but also stablizes the double bond character in the transition state.

Since the pyrolysis of ketones required such high temperatures, the reactions are not as clean as the pyrolysis of esters. The cleavage takes place at temperatures at which competing reactions, usually free-radical reactions, also occur. The formation of many of the by-products usually can be rationalized by the operation of radical chain reactions. In other words, these pyrolyses undoubtedly represent a competition between the concerted retro-ene reaction and homolytic bond breaking processes. Thus it appears that the pyrolysis of ketones will be of synthetic utility only for those ketones that have some degree of internal strain to promote decomposition or that contain some group that will stabilize the products.

Experimental Section[28]

Pyrolysis of 2,6-Heptanedione. An adaptation of procedures which appear in the literature[25,26] was used to synthesize the 2,6-heptanedione. From 478 g (4.46 mol) of 2,6-dimethylpyridine, 1850

mL of anhydrous methanol, 103 g (4.46 g-atoms) of sodium, and 335 g (4.83 mol) of hydroxylamine hydrochloride in 600 mL of 50% ethanol was obtained 47.4 g (46% yield based on sodium) of 2,6-heptanedione dioxime, mp 79–82 °C (reported[26] mp 83.4–84.6 °C). When 10.5 g (0.66 mol) of 2,6-heptanedione dioxime dissolved in 115 mL of 10% aqueous sulfuric acid was treated with a solution of 9.2 g (0.132 mol) of sodium nitrite in 15 mL of water, 3.5 g (42%) of 2,6-heptanedione, bp 48 °C (0.5 mm), mp 31–33 °C (reported[26] bp 48–50 °C (1.0 mm), mp 31–33 °C), was obtained.

A Hoskins Type FD303-A electric furnace, permanently clamped in a vertical position in a rack and equipped with an iron–constantan thermocouple and a potentiometrically calibrated pyrometer, was fitted with a 1 × 20 in. Vycor tube fitted with a standard taper $^{24}/_{40}$ outer joint at the top, a $^{1}/_{4}$ × 2 in. side-inlet tube near the top, and a standard-taper $^{24}/_{40}$ inner joint at the bottom, and packed to a depth of about 6.5 in. with Vycor chips. An inert atmosphere was maintained in the pyrolysis tube by the introduction of a slow stream of dry oxygen-free nitrogen. The pyrolysate was initially cooled by a 6-in. water-cooled spiral condenser and collected in a 5.5-in. test tube immersed in a dry ice–methyl Cellosolve bath. Attached between the condenser and the test tube by means of $^{24}/_{40}$ standard-taper joints was a two-way connecting tube with a side-arm suction tube. The material which did not condense in the test tube passed through the connecting tube into two condenser traps immersed in a dry ice–methyl Cellosolve bath and then into a tube containing a solution of bromine in carbon tetrachloride.

The 2,6-heptanedione (3.5 g) to be pyrolyzed was placed in a 10-mL separatory funnel and the ketone was dropped through the pyrolysis tube heated at 650 °C at the rate of 20 drops/min, while the tube was flushed with dry oxygen-free nitrogen (90 bubbles/min) to minimize oxidation and charring. Examination of the tube after pyrolysis indicated very little charring had taken place. The water-white pyrolysate which was collected amounted to 2.6 g. Weighed amounts of benzene and 2-octanone were added to the pyrolysate to serve as internal standards for the chromatographic analysis of the mixture. Known mixtures of benzene with acetone and methyl vinyl ketone as well as known mixtures of 2-octanone and 2,6-heptanedione were calibrated with regard to retention times and quantitative area responses. From a chromatographic analysis of the pyrolysate, it was shown to contain acetone (22%), methyl vinyl ketone (17%), and 2,6-heptanedione (66%). The yield of acetone and methyl vinyl ketone, based on unrecovered starting diketone, was 61 and 45%, respectively. No other products were found in the pyrolysate or in the bromine–carbon tetrachloride trap. When pyrolyses were attempted at 570 and 625 °C, little or no cleavage occurred.

Pyrolysis of Methyl Neopentyl Ketone. A modification of the procedure of Mosher and Cox[27] was used to prepare methyl neopentyl ketone. In a 5-L three-necked flask equipped with a mechanical steel stirrer, a dropping funnel, and a reflux condenser were placed 1179.6 g (4 mol) of potassium dichromate and 800 mL of water. To the reaction mixture was added 336.6 g (3 mol) of technical diisobutylene (80% 2,4,4,-trimethyl-1-pentene), bp 101–103 °C, n^{25}_{D} 1.4067 (reported[27] bp 101–104 °C, n^{25}_{D} 1.4060), followed by the addition of 1569 g (16 mol) of concentrated sulfuric acid with vigorous stirring over a period of 5 days. The temperature of the reaction mixture was maintained at 25–30 °C by the rate of addition of sulfuric acid, and then stirring was continued for an additional day. After steam distillation of the reaction mixture and drying of the distillate over magnesium sulfate, 240.5 g of crude methyl neopentyl ketone was obtained. Careful fractionation of the crude product through a 24-in. helix-packed column yielded 128 g (47%) of methyl neopentyl ketone, bp 123–125 °C (760 mm), n^{25}_{D} 1.4008 (reported[27] bp 124–125 °C, n^{25}_{D} 1.4018).

Anal. Calcd for $C_7H_{14}O$: C, 73.62; H, 12.36. Found: C, 73.48; H, 12.28.

Chromatographic analysis of the ketone showed the presence of only one peak in the chromatogram.

When the methyl neopentyl ketone (10.3 g) was pyrolyzed at 660 °C at the rate of 22 drops/min through the apparatus described above, a water-white pyrolysate was collected and no charring occurred in the tube. A weighed amount of methyl ethyl ketone was added to the pyrolysate as an internal standard and the mixture was analyzed on a gas chromatograph as described previously. The pyrolysate was shown to contain acetone (17%), isobutylene (18%), methyl neopentyl ketone (61%), and unidentified materials (4%). The yields of acetone and isobutylene, based on unrecovered methyl neopentyl ketone, were 44 and 46%, respectively.

When the temperature of pyrolysis was 585 or 630 °C, practically no pyrolysis occurred and the starting methyl neopentyl ketone was recovered unchanged. A so when a temperature of 690 °C was employed, much greater quantities of low-boiling "fragmentation" products, which were presumably formed by free-radical reactions, were noted. Analysis of the material in the bromine–carbon tetrachloride trap indicated that practically no material was collected.

Pyrolysis of Methyl Isobutyl Ketone. Commercial methyl isobutyl ketone (Matheson Coleman and Bell) was carefully fractionated through an 8-in. helix-packed column to give a water-white chromatographically pure distillate, bp 114–117 °C (reported[29] bp 114–116 °C). In the apparatus just described, 3.87 g of methyl isobutyl ketone was added to the pyrolysis tube heated at 650–655 °C at the rate of 60 drops/min. After a weighed amount of methyl ethyl ketone was added as an internal standard, the mixture was analyzed on a gas chromatograph to indicate that the pyrolysate consisted of some propylene, isobutylene (8%), acetone (7%), and methyl isobutyl ketone (75%). Although some of the volatile materials passed into the bromine trap, the material in the bromine–carbon tetrachloride trap was worked up in the usual way and the resulting 1,2-dibromopropane was analyzed in a gas chromatograph with a weighed amount of 1,2,3-tribromopropane added as internal standard. The analysis indicated that a 10% conversion to propylene had occurred during pyrolysis. The yields of acetone and propylene, based on unrecovered methyl isobutyl ketone, were 38 and 40% respectively. Pyrolysis of methyl isobutyl ketone at 625 °C resulted in nearly complete recovery of starting material.

Pyrolysis of Methyl *n*-Propyl Ketone. Commercial methyl *n*-propyl ketone (Brothers Chemical Co.) was distilled through an 8-in. helix-packed column to yield a clear liquid chromatographically pure distillate, bp 100–103 °C (reported[29] bp 102 °C). In the apparatus just described 2.94 g of methyl *n*-propyl ketone was added at the rate of 20 drops/min to the Vycor tube heated at 650 °C with the pyrolysate being collected in a tube cooled in dry ice and the low-boiling olefins collected in a bromine–carbon tetrachloride trap. A weighed amount of benzene was added to the pyrolysate as an internal standard and the mixture was analyzed on a gas chromatograph which showed that the pryolysis gave acetone (5%), methyl vinyl ketone (4%), and recovered methyl *n*-propyl ketone (60%). Analysis of the bromine–carbon tetrachloride trap showed the production of ethylene (1%) and propylene (1%).

Pyrolysis of Acetone. When acetone was pyrolyzed at 650 °C in the apparatus described previously, chromatographic analysis of the pyrolysate showed only the presence of acetone in nearly a quantitative recovery.

Registry No.—2,6-Heptanedione, 13505-34-5; diisobutylene, 25167-70-8; methyl neopentyl ketone, 590-50-1; methyl isobutyl ketone, 108-10-1; methyl propyl ketone, 107-87-9; acetone, 67-64-1.

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Stereochemical Consequences of *C*-Methylation of 1-Methylphosphorinane and Its Sulfide and Oxide: A Carbon-13 and Phosphorus-31 Nuclear Magnetic Resonance Study[1]

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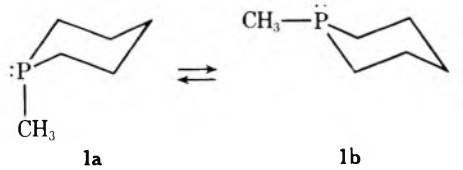
Placing a methyl at the 3 or 4 position of 1-methylphosphorinane results in conformational equilibria for both the cis and trans isomers that are strongly biased toward the form with equatorial *C*-methyl. This remains true when the phosphines are converted to sulfides, oxides, or methiodides. The steric demand of *C*-methyl is therefore considerably greater than that of *P*-methyl, a fact predicted for 1-methylphosphorinane by its $\Delta G°$ value of +0.35 kcal/mol. ^{13}C NMR spectroscopy was especially helpful in qualitatively analyzing the equilibria; the *C*-methyl and its carbon of attachment in a pair of isomers had little chemical shift variability, while *P*-methyl differed by 4–6 ppm, always with the axial methyl relatively upfield. Both the sulfides and the oxides have ring carbons 3 and 5 at higher field (2–3 ppm) when the sulfur or oxygen atoms are axial. This greater γ effect for a single-atom substituent on phosphorus over a methyl group has been observed previously for the case of S, but not for O. While ^{31}P NMR shifts were sensitive to the stereochemistry about phosphorus, no consistency in the direction of the effect was present. For the phosphines, axial methyl caused the expected relatively upfield shift. This was observed also for the sulfides, but the reverse effect prevailed for the oxides.

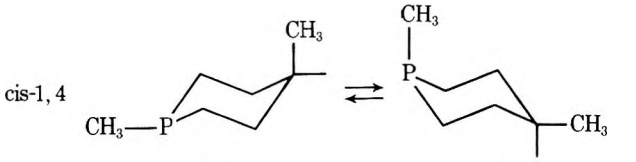
Phosphorus-substituted phosphorinanes are of considerable interest because of the predominance of the conformer with axial substituent over that with equatorial at room temperature.[2] For the 1-methyl derivative, the equilibrium constant (a ⇄ e) is estimated to be about 0.55, which gives $\Delta G°$ = +0.35 kcal/mol at 27 °C. This unusual result stems from a combination of a rather low enthalpy difference for the conformers ($\Delta H°$ = −0.68 kcal/mol) and a significant entropy effect ($\Delta S°$ = −3.4 eu). 1-Methylarsenane was later reported by another group to exhibit similar phenomena.[3] We have continued our investigation of the 1-methylphosphorinane system by considering the consequences of placing methyl at either the 3 or the 4 position, and then of adding sulfur, oxygen, or methyl to phosphorus to increase its covalency in these compounds. The synthesis and spectral properties of all of these compounds are reported in the present paper. Our major probe of the conformational changes occurring in these families has been ^{13}C NMR spectroscopy; we have previously employed this technique for hydroxy[4] and keto[5] derivatives of phosphorinanes and have witnessed a number of useful effects. ^{31}P NMR spectroscopy has also figured in our earlier studies and we have examined our new *C*-methyl compounds by this technique also.

The spectral data we have accumulated are best interpreted on the basis of perturbation of the conformational equilibrium for the parent 1-methylphosphorinane (**1**). Thus, a more

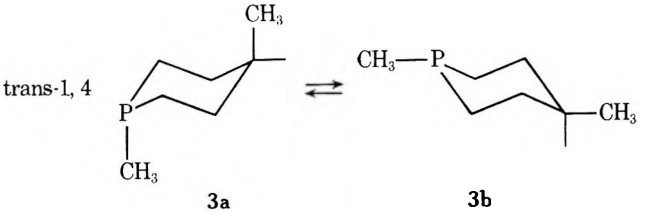


1a **1b**

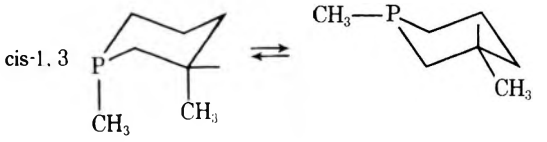
space-demanding group such as CH_3 ($\Delta G°$ = −1.7 kcal/mol in cyclohexanes; for thianes,[6] −1.80 ± 0.10 for 4-CH_3 and 1.40 ± 0.07 for 3-CH_3) placed on ring carbon 4 should control the equilibrium and the P-CH_3 group will be forced into greater occupation of the axial position (as in **2b**) in the cis isomer and of equatorial (**3b**) in the trans isomer. Similar consequences should result from methyl placed at the 3 position. Indeed, the principle of additivity of conformational free energies for remote substituents on a ring, most recently demonstrated to be valid in the related 1-methylthianium system,[7] should allow calculation of the position of these equilibria. For this purpose, we lack the $\Delta G°$ value for CH_3 on the phosphorinane ring, but



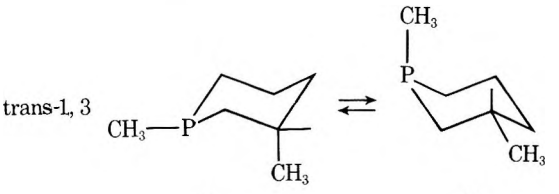
2a **2b**



3a **3b**



4a **4b**



5a **5b**

use of the cyclohexane value (−1.7) seems justified, which coupled with the value found for 1-methylphosphorinane (+0.35) leads to $\Delta G°$ = −2.05 kcal/mol for the *cis*-1,4-dimethyl system (**2**) and −1.35 for the *trans*-1,4-system (**3**). These values predict equilibrium constants of 92 and 9.9, respectively, or mixtures dominated by the *C*-methyl equatorial forms to a very large extent (99 and 91%, respectively). On comparing spectral properties for cis and trans forms, then, one should find significant differences about the P–CH_3 end, and considerable similarity at the C–CH_3 end. The same predictions would hold for the 1,3-dimethyl series, although we have refrained from making calculations in the absence of $\Delta G°$ for a 3-methyl group on this ring system.

When sulfur is added to 1-methylphosphorinane, it would be expected that a shift of the methyl group to the equatorial

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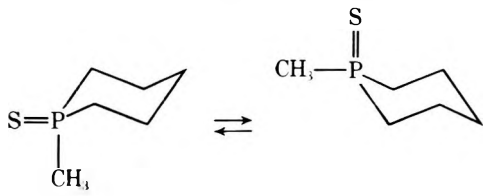
Table I. $^{13}C^{a}$ and ^{31}P NMR Spectra of 1,4-Dimethylphosphorinane and Derivatives

Compd no.	^{13}C-2,6	^{13}C-3,5	^{13}C-4	C-$^{13}CH_3$	P-$^{13}CH_3$	^{31}P-CH_3
2[b]	22.7 (14)	28.5 (0)[c]	34.1 (0)	23.5 (0)	5.7 (20)	−61.9
3[b]	28.5 (11)[c]	33.3 (6)	34.2 (0)	22.9 (0)	13.8 (18)	−55.7
7[d]	32.5 (50)	31.3 (7)	32.1 (0)	22.0 (0)[e]	15.9 (52)	+29.0
8[d]	31.1 (48)	28.8 (7)	32.7 (5)	22.0 (0)[e]	20.7 (52)	+30.8
11[d]	28.5 (63)	32.1 (6)	32.5 (5)	21.7 (0)[e]	12.0 (65)	+40.9
12[d]	27.6 (62)	29.0 (7)	32.3 (5)	21.7 (0)[e]	15.6 (66)	+38.7
15[f]	21.6 (50)	30.2 (5)	32.9 (7)	23.1 (0)	6.5 (55), 9.8 (55)	+17.2

[a] Values in parentheses are ^{13}C–^{31}P coupling constants in hertz. [b] ^{13}C spectrum neat; ^{31}P in benzene. [c] Overlapped signals. [d] Both spectra on $CHCl_3$ solutions. [e] Superimposed signals. [f] Both spectra on H_2O solutions; CH_3OH as internal ^{13}C reference.

position would occur. In this case of tetrahedral phosphorus, no mechanism is available to relieve the strain of 1,3-nonbonded interactions as is possible for the trivalent (pyramidal) system through expansion of bond angles.[2] Consequently, competition for the less crowded equatorial position should be won by the larger CH_3 group. This concept has already been tested and supported in other derivatives of phosphorinanes.[4a] Indeed, in another study in this Department directed by Professor A. T. McPhail,[8] it has been found by x-ray analysis of the crystalline 1-methylphosphorinane 1-sulfide that the methyl group is equatorial (**6b**). It is more difficult in advance



6a **6b**

of experimentation to predict what will occur when 3- or 4-CH_3 is placed on the ring with phosphorus in the tetrahedral condition, but as will be seen, the spectral data clearly reveal the control of the equilibria once again by the preference of the C–CH_3 group for the equatorial position.

The 1,3- and 1,4-Dimethylphosphorinanes. Carbon-13 NMR data for these compounds are conveniently discussed with reference to the 1-methyl parent, with two effects in mind: (1) replacement of ring hydrogen by methyl will produce the usual deshielding at α and β carbons and shielding at the γ carbon, by magnitudes dependent on axial–equatorial character; (2) the equilibria will shift so as to increase the axial P–CH_3 population in the cis compound of the 1,4 system and in the trans compound of the 1,3 system; it is quite clear from our earlier studies on hydroxyphosphorinanes[4] that axial P–CH_3 compounds have relatively upfield shifts at C-2,6, C-3,5, and at P–CH_3 due to steric crowding compared to the equatorial P–CH_3 compound. Indeed, these effects were used to assign cis,trans structure to the 1,4-dimethyl isomers that were obtained in unequal amount by the synthetic method used (CH_3PCl_2 added to the di-Grignard reagent of 1,5-dibromo-3-methylpentane). It is immediately evident from the ^{13}C spectra (Table I) that the isomers have nearly identical shifts for C-4 and for CH_3 on C-4, but that C-2,6 and C-3,5, as well as P–CH_3, are all markedly upfield in one (the minor) isomer. This leaves no doubt that both isomers have preferred conformations with equatorial C–CH_3 and that the minor isomer has the cis structure with a predominance of P–CH_3 axial (**2b**) and the major isomer is trans with a predominance of P–CH_3 equatorial (**3b**).

Comparison of the spectrum of *cis*-1,4-dimethylphosphorinane to that of the 1-methyl compound shows the following effects. (1) P–CH_3 is shifted upfield by 5.2 ppm; this is obviously the result of the increase in axial character of PCH_3 in the dimethyl compound (**2b**). (2) C-2,6 are also shifted upfield (4.0 ppm) by the increased axial P–CH_3 character (this upfield shift is not due to a γ effect of the 4-CH_3, since this is negligible for an equatorial group in cyclohexanes).[9] (3) C-3,5 feel opposite effects; they are shielded by the increased P–CH_3 axial character, but deshielded by the β effect of C–CH_3. The result is net deshielding (4.1 ppm). This is not unexpected, for the β effect of equatorial methyl on cyclohexane is a sizeable 8.9 ppm[9] and will dominate over the shielding. There is a marked difference in the ^{13}C–^{31}P coupling constant which also indicates the increased axial P–CH_3 character; there is no observable splitting in the dimethyl compound, while a doublet with J = 3 Hz is present for the 1-methyl compound. We have observed such stereodependence of $^2J_{PC}$ before,[2] and consistently have found that the value is largest (~6–7 Hz) with equatorial PCH_3 and is only 0–1 Hz in the axial case, as in the conformationally frozen 1-methyl-4-*tert*-butyl-4-phosphorinanols.[2] (4) C-4 is deshielded by the α effect of CH_3; the value (5.8 ppm) is nearly identical with the α-equatorial effect seen in cyclohexanes (5.6 ppm[9]).

The spectrum of the trans-1,4 isomer can be analyzed in the same way. (1) For PCH_3, there is increased equatorial character (**3b**) and consequently a downfield shift (2.9 ppm) relative to the 1-methyl case. (2) At C-2,6, there should also be deshielding accompanying the increased equatorial P–CH_3 character; the observed downfield shift is 1.8 ppm. (3) At C-3,5, deshielding is caused by both the increased equatorial P–CH_3 character and the β effect of the equatorial C–CH_3. The observed shift is 9.9 ppm. The expected increase in $^2J_{PC}$ also occurs; the value (6 Hz) is close to that (7 Hz) observed when P–CH_3 is frozen in the equatorial position in the 4-*tert*-butyl-4-phosphorinanol system.[2]

The chemical shift of the 4-CH_3 group in both isomers is very similar to that of 1-methylcyclohexane (δ 23.20[9]) and 4-methylthiane (δ 23.07[6]). That the shifts are not identical for the isomers, however, suggests that (1) the degree of equatorial character, while very large, is not precisely the same, and (2) the δ effect of the phosphorus function (+0.7 ppm in chain compounds[10]) is dependent on the configuration about phosphorus and is more important in the cis compound.

It is observed that some of the parameters (e.g., for P–CH_3 and C-2,6) for 1-methylphosphorinane fall between the extremes of the *cis*- and *trans*-1,4-dimethylphosphorinanes. Qualitatively, this is exactly what is expected for equilibria biased by *C*-methyl. It is not possible to use the data for quantitative conformational analysis, however, since the 4-methyl group is not an adequate anchoring group. Furthermore, the 4-methyl group clearly has an influence on the chemical shift of the phosphorus atom (vide infra) that may well be transmitted to carbons attached to phosphorus. To determine a conformational equilibrium constant by the chemical shift method requires assurance that a 4-substituent effect is absent.[11]

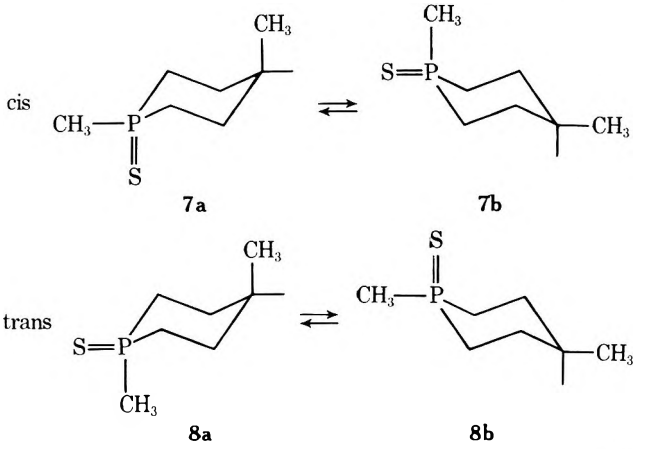
The synthesis of the 1,3-dimethylphosphorinanes proceeded similarly from the di-Grignard reagent of 1,5-dibromo-2-methylpentane. Again the cis and trans isomers were

formed in unequal amount. Here the cis isomer will have equatorial P–CH_3, in an equilibrium controlled by the greater demand of C–CH_3 for the equatorial position (**4b**), while the trans isomer will have axial P–CH_3 (**5b**). The differences in the P–CH_3 signals (major δ 14.3; minor δ 6.8) are immediately explainable on this basis and reveal the major isomer to have cis structure (**4b**). The similarity seen in the C–CH_3 signals (**5b**, δ 26.2; **4b**, δ 25.2) is then rationalized. These chemical shifts are noticeably downfield of those of the 1,4-dimethyl compound and we attribute this to the fact that phosphorus, rather than carbon, now occupies a γ position relative to 3-methyl. From our earlier study of open-chain phosphorus compounds, we know that trivalent phosphorus (as in the $(CH_3)_2P$ group) has a γ-shielding effect of only 0.5 ppm, while CH_3 has an effect of 2.4 ppm, a difference similar to that now seen on comparison of a 1,4- to a 1,3-dimethylphosphorinane with comparable disposition of the *P*-methyl group. Some other features of the spectra of these isomers are also notable. (1) C-2 and C-6 are easily recognizable in both isomers by the size of the coupling to ^{31}P. Of these, C-2 is the more deshielded due to the β effect of 3-methyl (about 5–6 ppm). The shift at C-6 is not influenced by the 3-methyl; the downfield shift noted in the cis isomer relative to the trans is due to the increased equatorial character of P–CH_3. (2) C-4 in both isomers, easily assigned by the absence of ^{31}P coupling, is strongly deshielded by the β effect of the 3-CH_3, about 10 ppm in each isomer relative to the 1-methyl compound. It is thus seen that the β effect of CH_3 is larger at C-4 than at C-2, but this effect has been found for 3-methylthiane also.[6] (3) C-5 is sensitive to two effects. The increased crowding due to P–CH_3 acquiring greater axial character is responsible for the noticeably upfield value for the trans isomer (δ 20.4) relative to the 1-methyl (δ 23.4), while relief of this crowding due to increased equatorial character of P–CH_3 in the cis isomer accounts for the downfield shift observed (δ 25.5). The value for $^2J_{PC}$ again supports these assignments; the isomer with axial P–CH_3 has the expected small constant (2 Hz), while the isomer with equatorial PCH_3 has the larger value (8 Hz). (4) The effect of CH_3 on C-3 is remarkably large for both isomers; relative to the 1-methyl compound, shifts of 13–14 ppm are observed. This shift greatly exceeds the expected α effect (5.8–5.9 ppm) seen in the 1,4-dimethyl compounds. The difference cannot be accounted for on any of the usual grounds; reassignment of the shifts to other carbons does not lead to any better interpretation.

The ^{31}P NMR shifts[12] (in benzene) for the axial P–CH_3 isomers (**2b**, −61.9; **5b**, −55.4) in each of the 1,4- and 1,3-dimethyl sets are upfield of the equatorial P–CH_3 isomers (**3b**, −55.7; **4b**, −54.3). This is the expected relation, based on our earlier studies with other phosphorinane derivatives,[2,4a] and is in common with the effects felt at ring carbon in cyclohexanes. However, the effect is noticeably more pronounced in the 1,4 isomers. the effect has not been considered previously for any 3-substituted phosphorinane, although it is known[13] for the 1,3-dimethylphospholanes that the difference in the cis and trans forms is small (δ −33.8 and −35.4, unassigned). In the 1,2-dimethylphospholenes,[13] the effect is actually reversed; the more crowded cis form (−16.7) is downfield of the trans (−28.2) and it would be of interest to determine values for the 1,2-dimethylphosphorinanes. Our attempts to prepare these compounds by the di-Grignard method have so far been unsuccessful, however. Another ^{31}P NMR feature of note is that the value[2] for 1-methylphosphorinane (neat, δ −53.7) falls outside the range for both of the pairs of dimethyl compounds, even allowing for the medium difference, and it is obvious that ^{31}P is influenced by other factors than just the degree of axial–equatorial character about the substituent it bears.

Sulfides of the Dimethylphosphorinanes. Addition of sulfur to the isomeric mixtures of 1,3- and 1,4-dimethylphosphorinanes produces the corresponding mixtures of 1-sulfides in good yield with retention of the isomer ratio. The effects on carbon of the conversion $R_3P \rightarrow R_3PS$ have been discussed in detail elsewhere;[4,10] the present discussion will concentrate on conformational effects only, as will that on the oxides and methiodides subsequently.

The 1,4-dimethyl isomers can be expected to participate in the conformational equilibria shown below (**7a,b, 8a,b**).



That the ^{13}C shifts (Table I) are virtually the same in both isomers for C-4 and for 4-CH_3 clearly indicates that the equilibria are dominated by the same structural effect, presumably that of equatorial 4-CH_3 (**7b** and **8b**). This is confirmed by the observation that P–CH_3 and C-3,5 are quite different in the isomers. The former signals (δ 15.9 and 20.7) fall close to values established for conformationally frozen models with axial and equatorial P–CH_3 (1-methyl-4-*tert*-butyl-4-phosphorinanol 1-sulfides:[4b] P–CH_3 axial δ 14.5; P–CH_3 equatorial, δ 20.5). The C-3,5 signals should then differ because of the stronger shielding of axial sulfur than of axial methyl, an unusual effect observed earlier,[4b] and indeed that isomer assigned structure **8b** from the P–CH_3 effect has the expected upfield signal (δ 28.8 vs. 31.3).

The above interpretation implies that the conformational free energy of CH_3 on carbon is substantially larger than CH_3 on phosphorus bearing sulfur, just as it is on trivalent phosphorus, or conversely that of sulfur on phosphorus bearing CH_3. We have earlier[4a] considered the relative influence of CH_3 vs. S on the conformational equilibrium of 1-methylphosphorinane 1-sulfide and predicted that the conformer with equatorial CH_3 (**6b**) would be in predominance. X-ray analysis later confirmed this predominance for the solid state.[8] That there could be a substantial amount of the conformer with axial CH_3 (**6a**) in solution remains a possibility, however, and is indeed indicated by the fact that the P–CH_3 signal (δ 18.5) falls between the extremes of the two 1,4-dimethyl isomers. Were P–CH_3 in **6** very largely in the equatorial position, a value more like that of the trans compound (**8b**) should have been observed.

Analysis of the ^{13}C NMR data (Table II) for the 1,3-dimethyl compounds points to the same conclusion of control of the conformational equilibrium by the C–CH_3 group. Thus, the isomers have very similar shifts for C–CH_3 and for C-4, but quite different ($\Delta\delta$ 5.3 ppm) values for P–CH_3. Also, the greater γ-shielding effect of axial sulfur, relative to axial CH_3, is evident at both C-3 and C-5 in the isomer suspected to prefer structure **9b**.

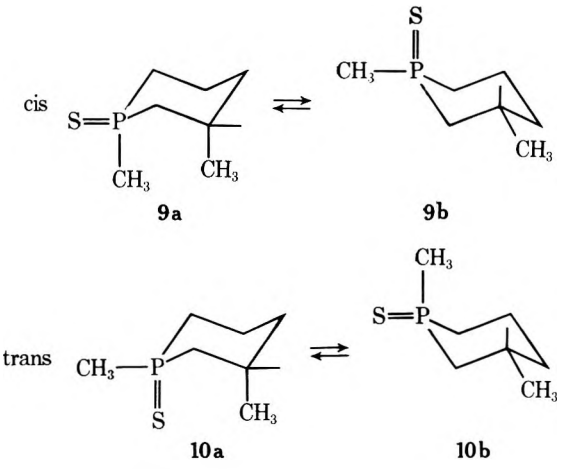
Another effect is present in both the 1,4 and 1,3 compounds: when sulfur is predominantly equatorial, small but noticeable deshielding occurs at the adjacent ring carbons (1.9 ppm at C-2, 1.8 ppm at C-6) relative to the form with axial sulfur. An effect of just this magnitude has been observed in the sulfides of the 1,4-dimethyl-1-phosphorinanols.[4]

There are two three-bond ^{13}C–^{31}P couplings in each of **9** and

Table II. $^{13}C^{a}$ and ^{31}P NMR Spectra of 1,3-Dimethylphosphorinanes and Derivatives

Compd no.	^{13}C-2	^{13}C-3	^{13}C-4	^{13}C-5	^{13}C-6	C-$^{13}CH_3$	P-$^{13}CH_3$	^{31}P-CH_3
4[b]	32.0 (8)	37.1 (3)	37.8 (0)	25.5 (8)	28.5 (10)	25.2 (5)	14.3 (16)	−54.3
5[b]	31.4 (10)	36.2 (2)	38.3 (0)	20.4 (2)	26.2 (12)[c]	26.2 (2)[c]	6.8 (18)	−55.4
9[d]	39.3 (39)	27.6 (4)	35.1 (6)	20.5 (5)	30.6 (50)	24.2 (18)[e]	21.7 (53)	+32.6
10[d]	41.2 (43)	30.8 (5)	34.1 (5)	23.1 (5)	32.4 (49)	24.2 (18)[e]	16.4 (52)	+30.5
13[d]	36.6 (62)	28.1 (6)[f]	35.3 (6)	20.6 (7)	27.4 (66)	24.6 (16)[c]	16.2 (68)	+40.6
14[d]	37.3 (63)	31.5 (4)	34.5 (6)	22.9 (4)	28.1 (65)[e]	24.3 (17)[c]	12.3 (66)	+42.2
16[g]	28.9 (49)	30.1 (5)	34.7 (7)	22.1 (5)	21.0 (51)	25.2 (16)	6.8 (53), 10.0 (54)	+19.2

[a] Values in parentheses are ^{31}P–^{13}C coupling constants in Hz. [b] ^{13}C spectrum neat; ^{31}P in benzene. [c] Overlapped signals. [d] Both spectra on $CHCl_3$ solution. [e] Signals nearly superimposed. [f] Overlapped signals. [g] Both spectra on H_2O solutions with CH_3OH as internal ^{13}C reference. Resolution was poor for C-2 and C-3 and C-5 and C-6, but a spectrum obtained at 15.0 MHz on a JEOL FX-60 spectrometer gave excellent resolution of all peaks and confirmed the assignments.



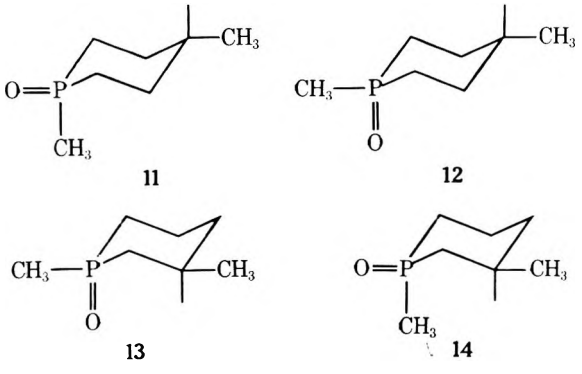
9a 9b

10a 10b

10, and a very large difference exists in their magnitude. The coupling to 3-CH_3 is a sizeable 18 Hz, while that to ring carbon 4 is only 5–6 Hz. We have previously noted a dihedral angle control of $^{3}J_{PC}$ in dimethylcyclohexylphosphine sulfides[14] and this appears to be the explanation for these phosphorinane derivatives as well. This effect will also be seen to prevail for the phosphine oxides and phosphonium salts to be discussed in later sections of this paper. The effect is useful in the present research since it supports the conclusion from chemical shift considerations that 3-CH_3 is in the same steric environment in both the cis and trans isomers.

The ^{31}P NMR shifts (in $CHCl_3$) for the sulfides of phosphorinanes are not as sensitive to structural changes as are those of the phosphines.[4a] Thus, the cis-1,4 compound (7) has δ +29.0 and the trans-1,4 compound (8) has δ +30.8. The 1-methyl compound falls out of this range (δ +33.9). For the 1,3-dimethyl compounds, similar values are found (9, +32.6; 10, +30.5). In both sets of isomers, the upfield shift is associated with the form exhibiting an axial P-CH_3 preference.

Oxides of the Dimethylphosphorinanes. Equilibria for the oxides resemble those for the sulfides, and the ^{13}C NMR data (Tables I and II) reveal again that C-CH_3 is dominant over the phosphorus function. Thus the cis (11) and trans (12)



11 12

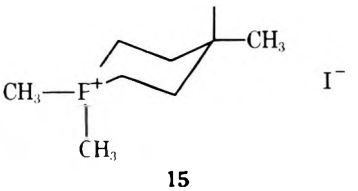
13 14

forms of the 1,4 compounds have very similar C-4 and 4-CH_3 signals, as do the cis (13) and trans (14) forms of the 1,3 compounds. The expected differences in the P-CH_3 signals are present. We have observed for the first time that the γ-shielding by axial oxygen exceeds that of axial CH_3, just as was true for sulfur. For the 1,4-dimethyl compounds, δ C-3,5 is 29.0 when axial oxygen is in predominance (12) and 32.1 for axial methyl (11). Similarly, for the 1,3-dimethyl compound with axial oxygen (13), δ C-3 (28.1) and C-5 (20.6) are upfield of the values for the isomer with axial CH_3 (14, δ C-3 31.5, δ C-5 22.9). The range for the axial oxygen effect is 2.3–3.1 ppm, which is like that of the axial sulfur effect (2.5–3.2 ppm). These shielding effects are clearly not interpretable on the usual basis of steric compression, and as we have pointed out elsewhere[4] probably require an explanation taking into account the polar character of the axial substituent.

The oxides also exhibit an effect at C-2 and C-6 like that seen for the sulfides compounds with equatorial oxygen consistently have these carbons at lower field than do those with axial oxygen.

The ^{31}P NMR shifts for the oxides (Tables I and II) show exactly the opposite relation as seen for the phosphines and the sulfides; greater shielding is associated with an equatorial, not axial, *P*-methyl group. While the cause of this reversal is not known at present, it is evident that ^{31}P NMR spectroscopy must be used cautiously in conformational analysis, since other exceptions may exist to the rule that in isomeric cyclic compounds upfield shifts are always associated with greater apparent 1,3-steric crowding. In the conformationally rigid 3,5-dimethyl-2-R-2-oxo-1,3,2-dioxaphosphorinanes, exceptions to the rule have also been encountered.[15]

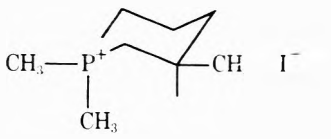
Methiodides of the Dimethylphosphorinanes. Based on the ^{13}C chemical shifts of C-4 and the 4-methyl group, which are found in the same region as the sulfide and oxide, it is possible to assign preferred conformation 15 to the methiodide



15

of 1,4-dimethylphosphorinane. If there was a significant amount of axial *C*-methyl, an upfield shift would have been noted. On the contrary, a weak deshielding due to the δ effect of the phosphorus function is seen. The *P*-methyl groups are nonequivalent; the axial CH_3 absorbs at higher field (δ 6.5) than the equatorial (δ 9.8).

The same spectral relations are found in the methiodide of 1,3-dimethylphosphorinane; the *C*-methyl group is assigned the equatorial position as in 16, since it is again slightly downfield of the position in the oxides and sulfides. Again



16

there is a substantial difference in the two P–CH_3 groups (δ 6.8 and 10.0).

Conclusions

^{13}C NMR spectroscopy is eminently suited for the determination of cis,trans structure in 1,4- and 1,3-dimethylphosphorinanes and in their sulfides and oxides as well. These spectral data are also compelling in pointing to the consistent preference of methyl on carbon 3 or 4 of the phosphorinane ring for the equatorial position in all structures studied, regardless of the phosphorus oxidation state, thus forcing *P*-methyl in some structures into the axial position. This is consistent with observations we have made previously[4] for 1,4-dimethyl compounds also bearing a 4-hydroxy group, where x-ray analysis provided unequivocal proof of structure. It is therefore implied that the net of nonbonded interactions for the two substituents on phosphorus in the sulfides and oxides must be of smaller magnitude than that of *C*-methyl, and it would be desirable to assess this competition on a quantitative basis by determining $\Delta G°$ values. Thus, groups such as $CH_3(S)P$ and $CH_3(O)P$ must have $\Delta G°$ values of size considerably smaller than the −1.7 kcal/mol assigned to 4-CH_3. This raises the question of relative preferences when 4-CH_3 is pitted against phosphorus functionalities having larger alkyl substituents than methyl. It is possible that the domination by 4-CH_3 will prevail for some of these groups, and great caution must be used in assigning configurations solely on group size parameters that are really applicable only when the groups are present on the cyclohexane ring. No data are presently available for such compounds, although the isomeric 1-phenyl-4-methylphosphorinane 1-oxides have recently been considered from a number of standpoints (not ^{13}C NMR) and the judgement has been made that *P*-phenyl is equatorial in both.[16]

The γ effect of ^{13}C NMR is frequently used to assign configurations to cis,trans isomers, although it is evident that the full nature of this effect is not well understood and at least for nonalkyl groups appears to have a component unrelated to group size.[17] We have previously seen[4] that axial P=S causes greater shielding at C-3,5 of the ring of the 4-phosphorinanols than does axial P–CH_3, and the present study is the first to report the same property for axial P=O in a pair of cis,trans isomers.[18] Another cautionary note is therefore required in the use of ^{13}C NMR for stereochemical assignment: relative "size" of the two substituents attached to tetracovalent phosphorus is not the sole factor causing shielding at γ ring carbons, and specific information about a particular system is required before the technique is useful. The problem does not exist, of course, for trivalent phosphorus, where an axial substituent routinely causes greater upfield shifts at C-3,5 than does an equatorial substituent.

^{31}P NMR has played an important role in studying conformational equilibria of 1-substituted phosphorinanes,[2] but it is now seen to have only limited utility in the *C*-methylphosphorinanes and in their sulfides and oxides. Thus, the chemical shift for 1-methylphosphorinane does not fall within the range set by the cis and trans isomers of 1,4-dimethylphosphorinane, as it should if the degree of axial and equatorial character were in control of the shift. Still, greater shielding of phosphorus does occur in the cis-1,4 and trans-1,3 isomers which have largely axial P– substituent, as has been observed for the individual conformers of 1-methylphosphorinane when examined at very low temperatures.[2] This is true also for the sulfides. For the oxides, however, it is the isomer with oxygen in the axial position that has the more upfield ^{31}P signal. ^{31}P NMR anomalies do exist among other related systems; in the oxides of the 1,3-dioxaphosphorinane system,[15] equatorial P=O usually, but not always, is associated with the more upfield ^{31}P NMR signal.

In spite of the anomalies in the ^{31}P spectra, methyl groups on phosphorus give ^{13}C signals that have invariably been of aid in assigning cis,trans structure. We have not yet encountered a case where the generality that an axial P–CH_3 falls upfield of an equatorial P–CH_3 is not observed, regardless of the phosphorus functionality, and this measurement is the method of choice in studying this stereochemical feature.

Experimental Section

General. All manipulations of phosphines were conducted in a nitrogen atmosphere in a glovebag. Melting points are corrected. Proton NMR spectra were taken on Varian A-60 or JEOL MH-100 spectrometers. Phosphorus NMR spectra were obtained with a Bruker HFX-10 spectrometer at 36.43 MHz, using the continuous wave technique with proton decoupling; shifts are referenced to prerun 85% H_3PO_4, with downfield shifts positive. Carbon NMR spectra were taken with the Bruker instrument at 22.62 MHz using the Fourier transform technique with proton decoupling; shifts are referenced to internal tetramethylsilane.

Interpretation of ^{13}C NMR Spectra. In both the 1,4- and 1,3-dimethylphosphorinane syntheses, unequal mixtures of the cis and trans isomers were obtained. The mixtures were used without separation in all spectral studies. Generally the complete set of peaks for each isomer could be observed with signals readily assigned to a particular isomer by the relative intensities. In the 1,4 compounds, signals for C-2,6 were obvious from their intensity and relatively large coupling to ^{31}P, while C-3,5 were revealed by their intensity and confirmed by their stereospecific coupling to ^{31}P. Other signals presented no difficulty. In the 1,3 compounds C-2 and C-6 were again recognized by their relatively large coupling to ^{31}P; the more downfield signal was assigned to C-2, since it experiences a β effect from the 3-methyl. This effect also shifts C-4 well downfield, making it an easily recognized singlet. Other carbons are also easily assigned. Similar reasoning sufficed to make assignments for the tetravalent derivatives, coupled with known shift effects at α, β, and γ carbons accompanying the conversion from trivalent phosphorus. These have been described elsewhere.[4,10] The spectra were sometimes quite complex, since two isomers were present and many signals were split. Occasional superposition or overlapping of lines occurred, making some assignments tenuous. These are noted in Tables I and II. No important uncertainties in the assignments remain, however.

3-Methyl-1,5-dibromopentane. A known procedure for the preparation of this compound from *N*-benzoyl-4-methylpiperidine and PBr_5 was used.[19] The product (43%) had bp 71–81 °C (0.8 mm) [lit.[19] bp 59–61 °C (0.3 mm)].

***cis*- and *trans*-1,4-Dimethylphosphorinane (2 and 3).** The Grignard reagent was prepared from 48.8 g (0.20 mol) of 3-methyl-1,5-dibromopentane and 12.8 g (0.50 g-atom) of magnesium in 300 mL of anhydrous ether. To the reagent was added a solution of 23.4 g (0.20 mol) of methylphosphonous dichloride in 50 mL of ether. After the exothermic reaction had subsided, the mixture was stirred overnight and then hydrolyzed with saturated NH_4Cl solution. The organic layer was collected and the aqueous layer was extracted with four 80-mL portions of ether. The combined ether solutions were dried ($MgSO_4$) and distilled to give 2.5 g (10%) of product at 68–74 °C (45–49 mm). The ^{31}P NMR spectrum (benzene)

showed the presence of both the cis (**2**, δ −61.9, 35%) and trans (**3**, δ −55.7, 65%) isomers. The ^{1}H NMR spectrum was uninformative, consisting of highly complex signals clustered at δ 0.74–1.00 (P–CH_3 and C–CH_3) and 1.00–2.22 (ring protons). No attempt was made to separate the isomers. ^{13}C NMR parameters obtained for the mixture are reported in Table I.

***cis*- and *trans*-1,4-Dimethylphosphorinane 1-Sulfide (7 and 8).** A solution of 1.0 g (0.008 mol) of the mixture of phosphines **2** and **3** in 20 mL of benzene was treated with 0.4 g (0.013 mol) of sulfur. The mixture was refluxed for 3 h and filtered while hot to remove unreacted sulfur. Evaporation of solvent left a crystalline residue which was purified by vacuum sublimation to give a product of wide melting range (71–94 °C) because of the presence of isomers. The mixture was analyzed directly.

Anal. Calcd for $C_7H_{15}PS$: C, 51.82; H, 9.32; P, 19.09. Found: C, 51.53; H, 9.15; P, 18.97.

^{1}H NMR ($CDCl_3$) δ 1.71 (d, $^2J_{PH}$ = 13 Hz, P–CH_3 for both isomers), 0.95 (d, $^3J_{HH}$ = 6 Hz, C–CH_3 for both isomers), 1.28–2.40 (m, ring protons); ^{31}P NMR ($CHCl_3$) δ +29.0 (cis (**7**), 32%) and +30.8 (trans (**8**), 68%); ^{13}C NMR, Table I.

***cis*- and *trans*-1,4-Dimethylphosphorinane 1-Oxides (11 and 12).** A 0.8-g sample of the mixture of phosphines **2** and **3** was stirred with 10 mL of 3% hydrogen peroxide for several hours. The solution was extracted with chloroform; the extract was dried ($MgSO_4$) and evaporated to leave a colorless liquid (0.6 g, 67%): ^{1}H NMR ($CHCl_3$) δ 0.88–1.12 (m, C–CH_3 for both isomers), 1.53 and 1.57 (both d, $^2J_{PH}$ = 13 Hz, P–CH_3 for both isomers), 1.44–2.88 (m, ring protons); ^{31}P NMR ($CHCl_3$) δ +40.9 (cis (**11**), 33%) and +38.7 (trans (**12**), 67%); ^{13}C NMR, Table I.

1,1,4-Trimethylphosphorinanium Iodide (15). The salt was prepared in ether from the mixture of phosphines **2** and **3** and methyl iodide; the product recrystallized from chloroform–hexane began to darken near 200 °C and decomposed sharply at 313 °C: ^{1}NMR (Me_2SO-d_6) δ 0.92 (d, $^3J_{HH}$ = 6 Hz, C–CH_3), 1.94 (d, $^2J_{PH}$ = 14 Hz, P–CH_3), 1.20–2.64 (m, ring protons); ^{31}P and ^{13}C NMR, Table I.

Anal. Calcd for $C_8H_{18}IP$: C, 35.33; H, 6.62; P 11.39. Found: C, 35.36; H, 6.14; P, 11.14.

2-Methyl-1,5-Dibromopentane. This compound was prepared by the same procedure used for the 3-methyl isomer, employing *N*-benzoyl-3-methylpiperidine. It was obtained in 38% yield: bp 76–78 °C (1.1 mm) [lit.[20] bp 110–112 °C (21 mm)].

***cis*- and *trans*-1,3-Dimethylphosphorinane (4 and 5).** These compounds were prepared by the same procedure used for the 1,4-dimethyl isomers (**2** and **3**), employing 48.8 g (0.20 mol) of 2-methyl-1,5-dibromopentane and 12.8 g (0.50 g-atom) of magnesium in 300 mL of ether for di-Grignard preparation and 23.4 g (0.20 mol) of methylphosphonous dichloride. The product (5.4 g, 21%) distilled at 81–85 °C (57 mm). The ^{1}H NMR spectrum (C_6H_6) was uninformative (overlapping P–CH_3 and C–CH_3 at δ 0.68–1.00, ring H at 1.13–2.00); ^{31}P NMR (C_6H_6) δ −55.4 (trans (**5**), 41%) and −54.3 (cis (**4**), 59%); ^{13}C NMR, Table II.

***cis*- and *trans*-1,3-Dimethylphosphorinane 1-Sulfides (9 and 10).** The mixture of phosphines **4** and **5** was sulfurized as before; after vacuum sublimation, the isomeric sulfide mixture had mp 43–58 °C and was analyzed as such.

Anal. Calcd for $C_7H_{15}PS$: C, 51.82; H, 9.32; P, 19.09. Found: C, 51.96; H, 9.43; P, 19.23.

^{1}H NMR ($CDCl_3$) δ 1.74 and 1.75 (both d, $^2J_{PH}$ = 13 Hz, P–CH_3 of both isomers), 0.96–1.18 (m, C–CH_3), 1.60–2.60 (m, ring H); ^{31}P NMR ($CHCl_3$) δ +32.6 (cis (**9**), 56%) and +30.5 (trans (**10**), 44%); ^{13}C NMR, Table II.

***cis*- and *trans*-1,3-Dimethylphosphorinane 1-Oxides (13 and 14).** The procedure used for the formation of **11** and **12** was applied to the mixture of phosphines **4** and **5**, forming a liquid product: ^{1}H NMR ($CHCl_3$) δ 1.54 and 1.55 (both d, $^2J_{PH}$ = 13 Hz, P–CH_3 of both isomers), 1.00–1.16 (two overlapping doublets, C–CH_3), 1.20–2.80 (m, ring H); ^{31}P NMR ($CHCl_3$) δ +40.6 (cis (**13**), 72%) and +42.2 (trans (**14**), 28%); ^{13}C NMR, Table II.

1,1,3-Trimethylphosphorinanium Iodide (16). Prepared by the method used for **15** as applied to the mixture of phosphines **4** and **5**, this compound had mp 213–214 °C after recrystallization from ethyl acetate–ethanol: ^{1}H NMR (Me_2SO-d_6) δ 1.04 (d of d, $^4J_{PH}$ = 3 Hz, $^3J_{HH}$ = 6 Hz, C–CH_3), 1.95 (d, $^2J_{PH}$ = 13 Hz, both P–CH_3 groups), 1.56–2.68 (m, ring H); ^{31}P and ^{13}C NMR, Table II.

Anal. Calcd for $C_8H_{18}IP$: C, 35.33, H, 6.62; P, 11.39; Found: C, 35.50, H, 6.52; P, 11.26.

Registry No.—**2**, 64999-61-7; **3**, 64999-62-8; **4**, 64999-63-9; **5**, 64999-64-0; **6**, 1661-16-1; **7**, 64999-65-1; **8**, 64999-66-2; **9**, 64999-67-3; **10**, 64999-68-4; **11**, 64999-69-5; **12**, 64999-70-8; **13**, 64999 71-9; **14**, 64999-72-0; **15**, 64999-73-1; **16**, 64999-74-2; 3-methyl-1,5-dibromopentane, 4457-72-1; methylphosphonous dichloride, 676-97-1; methyl iodide, 74-88-4; *n*-benzyl-3-methylpiperidine, 19202-02-9; 2-methyl-1,5-dibromopentane, 25118-31-4.

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Structures of Some of the Minor Aminoglycoside Factors of the Nebramycin Fermentation

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The structures of some of the minor factors of the nebramycin complex of antibiotics are elucidated through a combination of physical and chemical methods.

Nebramycin, a complex of aminoglycosides elaborated by *Streptomyces tenebrarius*, includes a number of factors showing broad-spectrum antibiotic properties. The structures of five of these aminoglycosides have been elucidated, largely through chemical and degradative studies.[1-3] More recently, these factors have been studied using ^{13}C[4,5] and ^{15}N[6] nuclear magnetic resonance (NMR) spectroscopies. Other laboratories have used ^{13}C NMR and mass spectrometry to assign structures to closely related aminoglycosides.[7-9] In the present paper, we discuss the use of these physical methods, in conjunction with improved techniques of isolation and purification, in elucidating the structures of eight minor factors isolated by various methods from the nebramycin fermentation medium.

Results

Structures of the nebramycin factors and derivatives to be discussed appear in Chart I. Elucidation of the structures of factor **2**,[3,5] factors **4**, **5**, and **5′**,[2] and factor **6**[1] has been discussed previously. Factors **8**–**10** were shown to be identical with the previously known aminoglycosides nebramine,[2] lividamine,[10] and neamine,[11] respectively, by chromatographic and spectrometric comparisons with authentic samples. Primary screening of bioactivity has shown that all factors have significantly less antimicrobial activity than do apramycin and tobramycin.

A portion of the mass spectral data collected in the course of this work is presented in Table I. Most of the factors gave satisfactory electron-impact mass spectra (EIMS) which could be interpreted by analogy to results with similar compounds.[8] A scheme which can be used to understand the major fragments observed in these spectra appears in Figure 1. Peaks at *m/e* 191, 163, 145, and 173 were very common (cf. fragments g–j, Figure 1). A peak at *m/e* 203 was common to tobramycin and kanamycin B and their derivatives; in the spectrum of tobramycin, accurate mass measurement allowed this fragment to be assigned the empirical formula $C_8H_{15}N_2O_4$. In factors **8**–**10**, which lack the second glycosidic unit at the 6-hydroxyl, the *m/e* 203 peak was weak or absent. We formulate this fragment as k (Figure 1), though of course the specific structure of the ion cannot be elucidated on the basis of the above evidence. It is interesting that an amine at carbon 3″ (i.e., $R_3 = NH_2$, Figure 1) seems to be essential to the origin of this ion, which is absent in the spectra of factors **3** and **12**.

A major fragmentation pathway results from disruption of the glycoside attached to O(4) of the deoxystreptamine unit, leading to fragments c–f. Analogous fragmentation of the other glycoside did not appear to be important in most cases. The *m/e* values of fragments a–f were useful in characterizing the substitution patterns throughout the molecules. While (M + 1) peaks were detectable in some cases, only field-desorption mass spectrometry (FDMS) yielded reliable molecular weight determinations, especially for the carbamate derivatives. The latter compounds yield EIMS which are very similar to those of the parent aminoglycosides. Finally, while apramycin (factor **2**) gave an EIMS which could be interpreted in terms of a fragmentation pattern analogous to that shown in Figure 1, the oxygenated factor **7** yielded only a FDMS. As a consequence, mass spectrometry could not be used to aid in the location of the extra oxygen atom of this factor.

^{13}C and ^{15}N NMR data for the nebramycin factors are collected in Table II. Peak assignments are based largely on previous work.[4-6] We regard the assignments of carbon resonances in the chemical-shift regions of 70–75 ppm in alkaline solutions and 65–75 ppm in acidic solutions to be tentative. Resonances of nitrogens 1, 3, 7′, and 4″ have been assigned on the basis of detailed titration experiments that are reported later. The variation in the chemical shifts of N(6′) in factors **3**, **4**, **5**, **5′**, **6**, **8**, **11**, and **12** is due to the very high pK_a of this nitrogen,[6] a fact not recognized until after many of these spectra were measured. Thus, variation of the pH of the solution from 9.5 to 11 effects a chemical-shift change of almost 2 ppm in this resonance.

Discussion

Factor 3. The molecular weight of factor **3**, as measured by FDMS, is 1 mass unit higher than that of factor **5** (kanamycin B). Such a circumstance would result if one of the amine functions of kanamycin B was replaced by hydroxyl. The ^{15}N NMR spectrum, in which only four nitrogen resonances were observed, supports this formulation. The EIMS shows that fragments b–f are all displaced 1 mass unit to higher mass, indicating that the 3-amino-3-deoxyglucose unit of kanamycin B has been replaced by a hexose. Therefore, factor **3** is identical with the previously reported aminoglycoside NK-1012-1.[12]

The ^{13}C NMR spectrum supports this conclusion. The peak at 55.1 ppm in the spectrum of kanamycin B, which has been assigned[4] to the 3″ carbon, has been replaced by a resonance in the 70–75-ppm region in the spectrum of factor **3**. Such a change is consistent with the replacemment of NH_2 with OH. When peaks characteristic of the 2-deoxystreptamine and 2,6-diamino-2,6-dideoxyglucose portions are subtracted from the ^{13}C NMR spectrum of factor **3**, the remaining six resonances accord well with the spectrum of the α-glucosidic moiety of methyl β-maltoside.[13] Additional NMR support of the proposed structure (Chart I) of factor **3** are the ^{15}N chemical shifts.[6]

Factor 7. Careful comparison of the ^1H NMR spectra of factors **2** and **7** led to the conclusion that the latter factor was 3′α-hydroxyapramycin (Chart I).[14] Other physical data are in full accord with this proposal. Thus, the FDMS of factor **7** indicates that its molecular weight is 555, i.e., 16 mass units higher than apramycin. The ^{13}C NMR spectrum contained 21 resonances, 3 of which occurred at chemical shifts typical of anomeric carbons. Furthermore, 12 of the carbon resonances accorded well with those assigned to the 4-amino-4-

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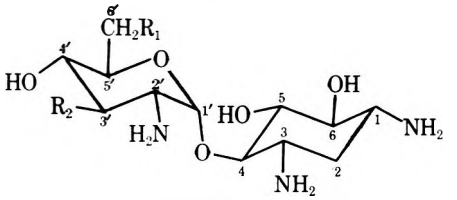
Table I. Mass Spectra of the Nebramycin Factors

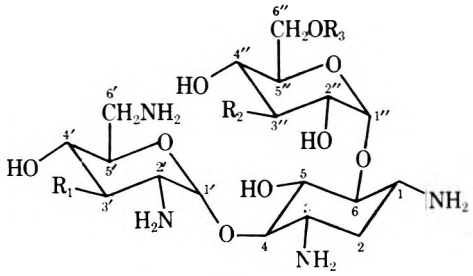
Factor	3	5	5′	6	8	9	10	11	12	13
Mol wt: FDMS[a]	484	483	510	467		307		510	468	510
EIMS (M + 1)	485	484		468	307	308	323		469	
a	161	161	145	145	145	146	161	145[b]	145	145[b]
b	163	162	162[b]	162				162	163	162
c	353	352	352[b]	352				352	353	352
d	325	324	324[b]	324				324	325	324
e	307	306	306[b]	306				306	307	306
f	335	334		334				334	335	

[a] The most intense peak in the FDMS occurs at M + 1. [b] Due to the facile loss of CONH during the EIMS process, peaks incorporating this moiety are not observed. [c] $C_{12}H_{27}N_4O_5$.

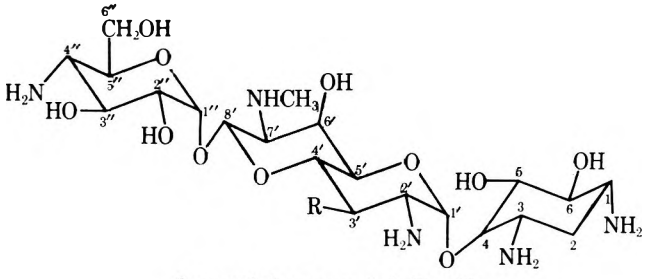
Chart I



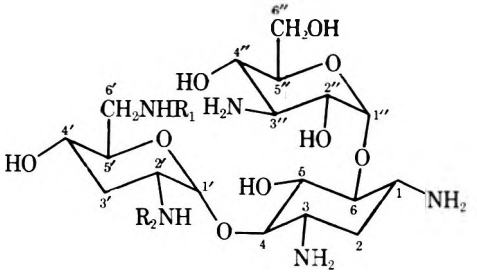
factor 8 (nebramine), $R_1 = NH_2$; $R_2 = H$
9 (lividamine), $R_1 = OH$; $R_2 = H$
10 (neamine), $R_1 = NH_2$; $R_2 = OH$



factor 3, $R_1 = OH$; $R_2 = OH$; $R_3 = H$
4, $R_1 = OH$; $R_2 = NH_2$; $R_3 = CONH_2$
5 (kanamycin B), $R_1 = OH$; $R_2 = NH_2$; $R_3 = H$
5′, $R_1 = H$; $R_2 = NH_2$; $R_3 = CONH_2$
6 (tobramycin), $R_1 = H$; $R_2 = NH_2$; $R_3 = H$
12, $R_1 = H$; $R_2 = OH$; $R_3 = H$



factor 2 (apramycin), R = H
7, R = OH



factor 11, $R_1 = H$; $R_2 = CONH_2$
13, $R_1 = CONH_2$; $R_2 = H$
Cbz-tobramycin A, $R_1 = CBz$; $R_2 = H$
Cbz-tobramycin B, $R_1 = H$; $R_2 = CBz$
Acetyltobramycin, $R_1 = COCH_3$; $R_2 = H$

deoxyglucose and 2-deoxystreptamine portions of apramycin. The remaining 9 resonances of the ^{13}C NMR spectrum of factors **2** and **7** are compared in Figure 2. It is seen from this comparison that the CH_2-3′ resonance of apramycin is replaced by a new peak in the 72–74-ppm region. In addition, peaks assigned to C-2′ and C-4′ [5] are shifted downfield by 4–6 ppm. Such changes are consistent with oxygenation at carbon C-3′.[4,5,15] It is also noted in Figure 2 that the remaining carbon resonances are relatively unchanged in the two factors, a result which is consistent only with an equatorial hydroxyl at C-3′. An axial hydroxyl at this position, for example, should lead to a shielding effect at C-1′. The ^{13}C data are therefore in full accord with the proposed structure[14] of factor **7**.

The ^{15}N NMR spectra of factors **2** and **7** are also characteristic of the differences in their structures. Of the five resonances of each spectrum, only one shows a significant change in chemical shift. This large upfield shift associated with hydroxylation is typical of the γ effect of an oxygen atom.[6]

Factor 11. Field-desorption mass spectrometry indicated that the molecular weight of factor **11** was the same as that of factor **5′**, suggesting that these two aminoglycosides were isomeric. This hypothesis was supported by the presence of peaks characteristic of a carbonyl group in both the infrared (1660 cm^{-1}) and the ^{13}C NMR (161.2 ppm) spectra. The positions of these peaks, however, differed significantly from those of the known carbamates, factors **4** and **5′**. In fact, the stretching frequency in the infrared spectrum seemed in better accord with those of ureido groups.[15] On these bases, it was concluded that factor **11** was a ureido derivative of tobramycin.

The EIMS of factor **11** was essentially the same as that of tobramycin and was therefore not useful in locating the carbonyl substituent. Comparison of the ^{13}C spectra of factor **11** and tobramycin, however, suggested that the 2-deoxystreptamine and 3-amino-3-deoxyglucosidic moieties of these two factors were identical. In contrast, resonances assigned to C-1′ and C-3′ in the spectrum of tobramycin were significantly shielded in that of factor **11**. It was therefore inferred that the N(2′) of factor **11** was attached to a carbonyl group. This conclusion was supported by the ^{13}C NMR spectrum of factor **11** in acidic solution (pH 3). Figure 3 shows that C-1′ and C-3′ of factor **11** are significantly deshielded relative to tobramycin, consistent with the absence of a β-protonation effect[4,5] due to the nonbasic nature of N(2′).

On the basis of our present evidence, we believe that factor **11** is the *N*(2′)-ureido derivative of tobramycin. In repeated attempts to measure the ^{15}N spectrum of this factor, however, only five resonances were observed. The missing resonance is believed to be that due to the $CONH_2$ group. Possibly the difficulty in observing this signal is due to one of the "nulling" mechanisms known to complicate ^{15}N NMR spectroscopy[16] or to the presence of trace amounts of paramagnetic ions.[17] The very limited amount of this factor has precluded further studies.

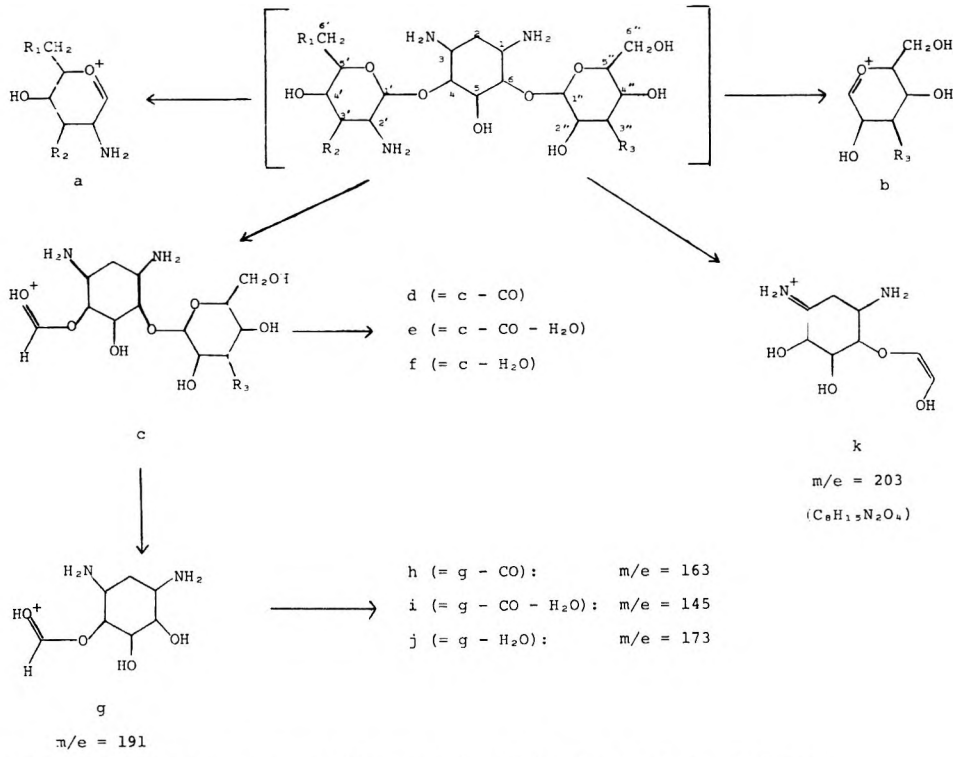


Figure 1. Representative electron-impact mass spectral fragmentation of the tricyclic nebramycin factors.

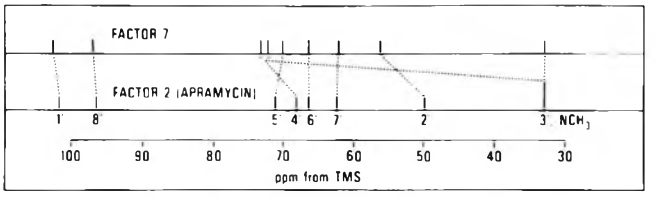


Figure 2. Comparison of the ^{13}C NMR spectra of the octose portions of apramycin and factor 7.

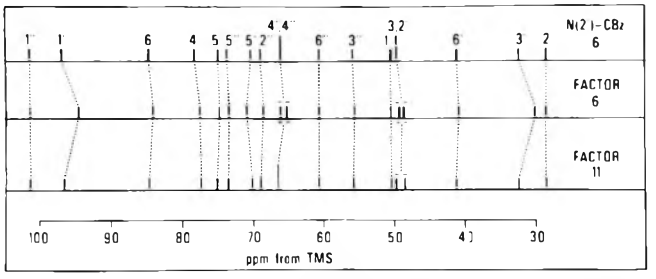


Figure 3. Comparison of the ^{13}C NMR spectra of $N(2')$-carbobenzoxytobramycin, tobramycin (factor **6**), and factor 11 in acidic solution (pH 3).

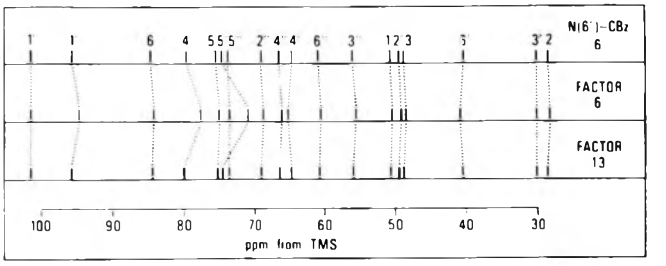


Figure 4. Comparison of the ^{13}C NMR spectra of $N(6')$-carbobenzoxytobramycin, tobramycin (factor **6**), and factor **13** in acidic solution (pH 3).

Factor 12. Both FDMS and EIMS indicate a molecular weight of 468 for this factor. Comparison of its spectra to those of the other members of the nebramycin complex suggests that this compound is a deoxygenated factor **3**. Thus, the ^{15}N NMR spectra of factors **3** and **12** both show four resonances, one appearing at a high-field position characteristic of an aminomethyl group.[6] The four resonances of the spectrum of factor **12** correspond well with the chemical shifts of the resonances of nitrogens 1, 3, 2′, and 6′ of tobramycin and nebramine, suggesting that this portion of the molecule is similar in these three factors. Both factors **3** and **12** show b fragments with *m/e* 163, indicating the presence of a hexosoyl moiety. Comparison of the ^{13}C NMR spectra of factors **3, 6,** and **12** confirms the assignment of the 3′-deoxy factor **3** structure to the last compound.

Factor 13. The molecular weight of this aminoglycoside is also shown by FDMS to be the same as that of factors **4, 5′,** and **11.** The presence of a carbonyl group is demonstrated by the ^{13}C NMR spectrum (resonance at 162.2 ppm) and by an infrared band at 1660 cm^{-1}; as indicated above, the latter datum is characteristic of a urea. Factor **13** was therefore proposed to be a ureidotobramycin.

Comparison of the ^{13}C spectrum of this factor with that of tobramycin shows that these two compounds must be very similar structurally. The only significant differences between the ^{13}C spectra of these factors are in the chemical shifts of carbons 4, 1′, 2′, and 6′. In acidic milieu (Figure 4), the resonances of the two methylenes (2 and 3′) in factor **13** and tobramycin have very similar chemical shifts, indicating that the ureido group cannot be located at positions 1, 3, or 2′. The chemical shift differences at carbons 4, 1′, and 2′ in these factors therefore cannot result from substitution at these positions. Possibly these changes result from differing conformations around the ether bonds linking the 2-deoxystreptamine and 2,6-diamino-2,3,6-trideoxyglucose moieties of these aminoglycosides.

Because of the absence of the β-protonation shift[4,5] at carbon 5′ when factor **13** is dissolved in acidic solution (Figure 4), we propose that this factor is 6′-ureidotobramycin. In support of this hypothesis is the close correspondence in the ^{13}C NMR spectra of factor **13**, $N(6')$-carbobenzoxytobramy-

Table II. ^{13}C and ^{15}N Chemical Shifts[a] of the Nebramycin Factors (ppm)

Carbon resonances	Factor[c] 2	3	4	5	5′	6	7	8	9	10	11	12	13	N(6′)-Acetyltobramycin[c]	6′-Cbz-tobramycin A[c]	2′-Cbz-tobramycin B[c]
1	51.1	51.2	51.4	51.2	51.5	51.2	51.1	51.1	51.3	51.2	51.0	51.2	51.3	51.4	51.5	51.2
2	36.6	36.3	36.2	36.2	36.5	36.5	36.6	36.6	36.6	36.5	36.3	36.4	36.5	36.6	36.8	36.5
3	50.3	50.2	50.1	50.1	50.1	49.9	50.1	50.3	50.5	50.1	50.2	50.3	50.1	50.2	50.5	50.5
4	87.8	87.6	87.1	86.7	87.4	87.3	88.1	87.7	88.1	88.0	87.3	87.0	88.2	88.7	89.0	88.3
5	76.8	75.2	75.0	75.2	75.1	75.3	76.8	76.8	76.9	76.8	75.0	75.3	75.3	75.4	75.6	75.1
6	78.4	88.8	88.3	88.5	88.6	88.7	78.3	78.5	78.4	78.3	89.3	89.0	88.7	89.0	89.2	89.2
1′	101.6	101.2	100.9	100.7	100.7	100.4	102.4	100.8	101.0	101.6	98.0	100.3	100.9	101.4	101.7	98.2
2′	49.8	56.2	56.1	56.1	50.4	50.2	56.1	49.9	50.0	56.1	49.7	49.9	50.6	50.7	50.9	50.9
3′	32.9	72.2	72.2	72.3	35.9	35.8	72.2	35.9	35.8	72.2	33.5	35.7	35.6	35.8	36.3	33.4
4′	67.9	72.7	73.0	72.9	67.1	67.0	73.1	67.0	65.5	73.9	66.6	67.0	67.0	67.3	67.3	66.7
5′	71.0	74.4	74.3	74.2	74.5	74.5	70.1	74.6	74.4	74.4	74.7	72.3	73.3	73.1	73.8	74.4
6′	66.2	42.4	42.3	42.3	42.6	42.6	66.3	42.5	61.7	42.5	42.3	42.4	41.8	41.3	42.8	42.5
7′	62.3						62.1									
8′	96.4						96.9									
NCH_3	32.9						32.9									
1″	95.3	101.2	100.6	100.7	100.4	100.7	95.9				100.8	101.3	100.8	100.9	101.1	100.9
2″	71.7	74.0	72.5	72.6	72.6	72.6	71.7				72.5	74.2	72.7	73.0	73.5	73.2
3″	74.2	72.5	55.0	55.1	55.2	55.2	74.3				55.0	72.5	55.3	55.2	55.5	55.2
4″	53.2	70.1	70.2	70.1	70.3	70.2	53.1				70.2	70.2	70.3	70.6	70.6	70.3
5″	73.4	74.0	71.1	72.9	71.0	73.0	73.4				73.1	73.9	73.0	73.0	73.0	72.7
6″	61.6	61.0	64.6	61.2	64.6	61.3	61.7				61.3	61.0	61.3	61.7	61.7	61.1
Others			$CONH_2$: 159.8		$CONH_2$: 159.9						$CONH_2$: 161.2		$CONH_2$: 162.2			
Nitrogen resonances																
1	8.2	7.7	7.6	7.9	7.9	8.0	8.0	7.9			7.6	7.9	7.9			
3	9.1	9.1	9.1	9.3	9.6	9.4	8.4	9.3			9.1	9.3	9.6			
2′	7.5	−1.0	−0.9	−0.8	7.5	7.4	−1.0	7.1			68.0[b]	7.3	7.4			
6′	–	−8.5	−8.5	−7.9	−7.5	−6.8	–	−7.7			−8.0	−7.0	52.3			
7′	−1.1	–	–	–		–	−1.2	–								
3′	–	–	1.1	1.2	1.3	1.3	–	–			1.0		1.3			
4′	0	–	–	–		–	0	–								
Others			$CONH_2$: 52.0		$CONH_2$: 52.3											

[a] ^{13}C chemical shifts are relative to external Me_4Si; ^{15}N shifts are relative to external NH_4Cl. All chemical shifts are measured at ca. pH 10. [b] This peak may be an instrumental artifact. [c] Registry no.: **2**, 37321-09-8; **3**, 31077-70-0; **4**, 51736-76-6; **5**, 4696-76-8; **5′**, 51736-77-7; **6**, 32986-56-4; **7**, 56283-52-4; **8**, 34051-04-2; **9**, 36019-33-7; **10**, 3947-65-7; **11**, 64332-33-8; **12**, 64332-34-9; **13**, 64332-35-0; N(6′)-acetyltobramycin, 61083-42-9; 6′-Cbz tobramycin, 50721-30-7; 2′-Cbz tobramycin, 64332-36-1.

cin, and N(6′)-acetyltobramycin. The structure of the last derivative has been determined through ^{15}N NMR spectroscopy.[6]

As in the case of factor **11**, the ^{15}N NMR spectrum of factor **13** showed five, rather than the expected six, resonances. The high-field resonance typical of the aminomethyl group was not present, confirming the hypothesis that this nitrogen had been acylated.

Carbobenzoxytobramycins A and B. Treatment of tobramycin in aqueous tetrahydrofuran (THF) with 1 equiv of *N*-(benzyloxycarbonyloxy)succinimide, followed by extensive chromatography, led to the isolation of two isomeric monocarbobenzoxylated derivatives of tobramycin. It is evident from Table II and Figures 3 and 4 that the ^{13}C NMR spectra of these compounds accord well with those of factors **11** and **13**. On this basis, carbobenzoxytobramycins A and B were identified as 6′-Cbz and 2′-Cbz derivatives, respectively.

***N*(6′)-Acetyltobramycin.** Treatment of an aqueous THF solution of tobramycin with 1 mol equiv of acetic anhydride led to the formation of a monoacetamide. From ^{15}N NMR spectroscopy, it was immediately evident that this derivative was N(6′)-acetyltobramycin.[6] Thus, of the five nitrogen resonances in the ^{15}N spectrum, only that assigned to N(6′) was significantly deshielded relative to tobramycin. Also in accord with the proposed structure is the ^{13}C NMR spectrum, which accords well with those of factor **13** and Cbz-tobramycin A (vide supra).

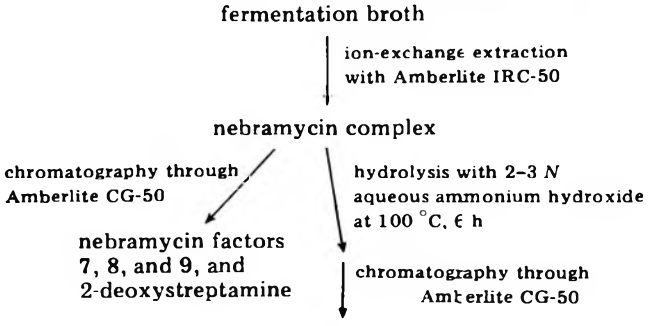
Experimental Section

^{13}C (25.03 MHz) and ^{15}N (10.09 MHz) NMR spectra were measured on a JEOL PFT-100 NMR spectrometer interfaced to an EC-100 data system. Full-proton decoupling was used in all measurements. The conditions of collection and transformation of spectra would be expected to lead to maximum line-broadening increments of 0.7 Hz for ^{13}C and 2 Hz for ^{15}H NMR spectra. Electron-impact mass spectra were obtained by direct ion-source introduction using a Varian-MAT Model 731 mass spectrometer at an ionizing energy of 70 eV. The same instrument was used to determine field-desorption spectra from carbon dendrite emitters.

Isolation and Purification of Nebramycin Minor Factors. The recovery of the crude nebramycin complex by ion-exchange extraction from the fermentation broth has been reported previously.[2] The separation of the complex has also been reported[2] and was accomplished by chromatography through Amberlite CG-50 resin.

Some of the new compounds, which include factors **7**, **8**, and **9**, and 2-deoxystreptamine, were isolated by direct chromatographic separation of the complex. Factors **3**, **10**, **11**, **12**, and **13** were separated from

Scheme I
Isolation and Purification of Nebramycin Minor Factors



the complex after mild basic hydrolysis. This hydrolysis was carried out with a 3–5% aqueous solution of the complex and 2–3 N aqueous ammonium hydroxide at 100 °C. The chromatography columns were eluted with aqueous ammonium hydroxide gradients. The direct separation of the nebramycin complex gave the following order of elution: nebramycin factors **7** and **9**, 2-deoxystreptamine, and nebramycin factor **8**. The separation of the hydrolyzed complex gave another elution sequence: nebramycin factors **13**, **3**, **11**, **12**, and **10**.

The chromatography fractions were identified by thin-layer chromatography. Thin-layer chromatography was performed on silica gel (60 F254, EM Laboratories, Inc.) using either a mixture of methanol/chloroform/28% aqueous ammonia in the volume ratio of 3:1:2 or an aqueous solution containing 1.5 mol of sodium acetate, 1 mol of sodium chloride, and 100 mL of *tert*-butyl alcohol per liter of solution.

Identical chromatography fractions were combined, freeze-dried, and dependent on the TLC result, either purified or rechromatographed. The overall isolation and purification sequence of the nebramycin minor factors is illustrated in Scheme I.

Nebramycin Factor 3. The combined and freeze-dried chromatography fractions were decolorized with carbon and crystallized from methanol. A white solid, $[\alpha]^{20}_D$ + 136°, was obtained. Hydrolysis with 3 N aqueous hydrochloric acid at 90 °C gave neamine, which was identified by thin-layer chromatographic comparison with an authentic sample.

Nebramycin Factor 7. The crude material was purified by crystallization from aqueous 1-propanol. A white solid, $[\alpha]^{20}_D$ +170°, mp >265 °C dec, was obtained. Anal. Calcd for $C_{21}H_{41}N_5O_{12}$: C, 45.39; H, 7.44; N, 12.61; O, 34.55. Found: C, 45.10; H, 7.53; N, 12.37; O, 34.82.

Nebramycin Factor 8. The freeze-dried chromatography fractions were decolorized with carbon and crystallized from methanol. A white solid, $[\alpha]^{20}_D$ +110°, mp >225 °C dec, was obtained. Anal. Calcd for $C_{12}H_{26}N_4O_5$: C, 47.05; H, 8.55; N, 18.27. Found: C, 47.07; H, 8.35; N, 17.92.

Nebramycin Factor 9. The dried material was decolorized with carbon and crystallized from a methanol/ethanol mixture. Recrystallization from methanol afforded a white solid, $[\alpha]^{20}_D$ +94°, mp 222–224 °C dec. Anal. Calcd for $C_{12}H_{25}N_3O_6$: C, 46.90; H, 8.20; N, 13.67. Found: C, 47.18; H, 8.46; N, 13.65.

Nebramycin Factor 10. The combined dried material was decolorized with carbon and crystallized from methanol. A white solid, $[\alpha]^{20}_D$ +123°, mp >300 °C dec, was obtained.

Nebramycin Factor 11. The crude material was decolorized with carbon and crystallized from methanol. A white solid, $[\alpha]^{20}_D$ +123.5°, was obtained. Hydrolysis with 3 N aqueous hydrochloric acid at 90 °C gave tobramycin, which was identified by TLC comparison with an authentic sample.

Nebramycin Factor 12. This compound was purified by crystallization from methanol. An almost white solid was obtained.

Nebramycin Factor 13. Crystallization from a methanol/ethanol mixture yielded an off-white solid.

2-Deoxystreptamine. The freeze-dried chromatography fractions were decolorized with carbon and crystallized from methanol. The white solid had no optical rotation and was identified by its spectral data and TLC comparison with an authentic sample.

Carbobenzoxytobramycins A and B. A solution of 25 g (0.054 mol) of tobramycin in aqueous THF was cooled to −3 °C. To this solution was added 14.7 g (0.059 mol, 1.1 mol equiv) of *N*-(benzyloxycarbonyloxy)succinimide in THF in five portions. The reaction was warmed to room temperature and allowed to stir for 90 min. The solution was concentrated and extracted with chloroform and 1-butanol. The extracted aqueous solution was loaded onto a Bio-Rex 70 (NH_4^+) column and eluted with a NH_4OH gradient; yields: 7.5 g (23%) of Cbz A; 0.6 g (2%) of Cbz B.

***N*(6′)-Acetyltobramycin.** A solution of 5 g (0.011 mol) of tobramycin in 6% THF/water was cooled to 0 °C. To this solution was added 1.1 g (0.011 mol) of acetic anhydride. The reaction mixture was maintained at −4 °C for 16 h and then allowed to come to room temperature for 24 h. The solution was concentrated and loaded onto a Bio-Rex 70 (NH_4^+) column which was eluted with a NH_4OH gradient; yield: 1 g (18%) of *N*(6′)-acetyltobramycin.

Registry No.—*N*-(Benzyloxycarbonyloxy)succinimide, 13139-17-8.

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Reactions of Ketene Acetals. 10.[1] Total Syntheses of the Anthraquinones Rubrocomatulin Pentamethyl Ether, 2-Acetylemodin, 2-Acetyl-5-hydroxyemodin Tetramethyl Ether, and Xanthorin

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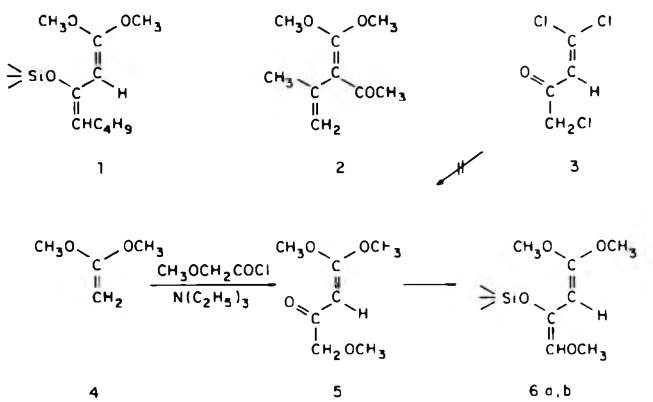
Some new or recently prepared conjugated ketene acetals such as 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene, 1,1-dimethoxy-3-trimethylsilyloxyocta-1,3-diene, and 2-acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene have been used in cycloaddition-type reactions for first or improved syntheses of the title compounds.

Conjugated ketene acetals[1-3] (1,1-dialkoxybutadienes) or the vinylogues of ketene acetals[4] have recently been used for the facile and regiospecific synthesis of a number of naturally occurring naphthoquinones and anthraquinones. These reagents have the advantage of being easy to prepare and quite reactive toward most quinonic substrates. Moreover they have been modified so as to introduce up to three groups with the desired orientation in a single annelating step. Some dienes previously obtained in this laboratory have now been applied to the synthesis of some highly substituted anthraquinones and a new reagent, 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene (**6a,b**), has been prepared in order to extend the scope and usefulness of the method (Scheme I).

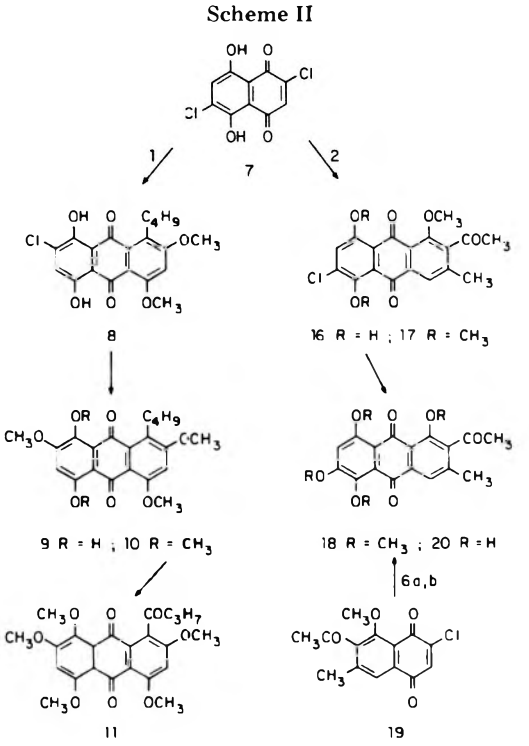
The synthesis of penta-*O*-methylrubrocomatulin (**11**), the tetramethyl ether of a crinoid pigment,[5] was attempted by first condensing 2,6-dichloronaphthazarin (**7**) with 1,1-dimethoxy-3-trimethylsilyloxyocta-1,3-diene[2] (**1**) (Scheme II). Pyrolysis of the adduct, hydrolysis of the silyl ether, and partial methylation gave a 56% yield of 1-butyl-7-chloro-5,8-dihydroxy-2,4-dimethoxyanthraquinone (**8**). Finally the remaining chlorine was substituted (76%) according to a recent procedure[6] using sodium methoxide and copper(I) iodide. Complete methylation of this trimethyl ether (**10**) under the usual conditions followed by photooxidation[2] as in the syntheses of rhodolamprometrin and rhodocomatulin provided rubrocomatulin pentamethyl ether, which was indistinguishable in all respects from a sample of the authentic material.

2-Acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene[1] (**2**), obtained earlier by us from pent-3-en-2-one and ketene dimethyl acetal for the preparation of stypandrone, has now been applied to the synthesis of two coccid pigments recently isolated by Banks and Cameron.[7] A first attempt at condensing the foregoing diene with 2-chloro-6,8-dimethoxynaphthoquinone[1] (**12**) in boiling benzene followed by pyrolysis at 135 °C produced no anthraquinonic material; however, bringing the components together in refluxing xylene gave a 50% yield of

Scheme I



Scheme II



the expected product 2-acetyl-1,6,8-trimethoxy-3-methylanthraquinone (**14**) (Scheme III).

It is now well established that 3-halojuglones are more reactive than the corresponding ethers toward ketene acetals and 1,1-dialkoxybutadienes and consistently produce higher yields. Consequently the 8-methyl ether of the chosen substrate (**12**) was cleaved by anhydrous aluminium chloride. The resultant juglone (**13**) reacted with the same diene (**2**) and gave a 78% yield of acetylemodin trimethyl ether (**14**) after methylation. This compound was then demethylated by a brief contact with a semisolid mixture of aluminium and sodium chlorides at 90 °C and yielded a substance which was indistinguishable from the natural product (**15**). A partial synthesis[8] of this compound had been carried out earlier starting from natural stypandrone.

The synthesis of another coccid pigment, 2-acetyl-5-hydroxyemodin (**20**), could at this point then be envisaged using the same diene and 2,6-dichloronaphthazarin (**7**) (Scheme II). The condensation of these two compounds proceeded smoothly and gave an 81% yield of 2-acetyl-6-chloro-5,8-dihydroxy-1-methoxy-3-methylanthraquinone (**16**). Substitution of the remaining chlorine by methoxide (followed by complete methylation) proved to be unexpectedly difficult, being accompanied by considerable decomposition. In an initial attempt the process was interrupted after 6 h; the product, after methylation, yielded mainly a derivative (**17**)

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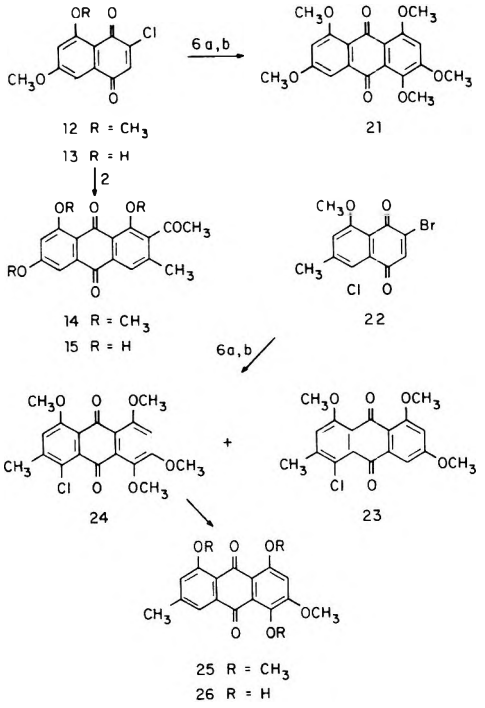
Scheme III



of the substrate (59%) and only 6% of the desired substance (**18**). By extending the reaction time to 12 h the substitution product could be increased to 13% while only 16% of the unreacted material could be recovered. Attempted demethylation of the tetramethyl ether as before gave a large number of products which were not isolated.

At this point a more satisfactory method of forming the 1,2,4-trihydroxylated ring was explored. In a first approach 1,4,4-trichlorobut-3-en-2-one (**3**) was obtained according to the procedure used for the 4,4-dichloro compound. It was expected that methoxydehalogenation involving all or, more selectively, the ethylenic chlorines could be realized; however, all attempts to carry out the substitutions yielded only intractable tars. On the other hand, the addition of ketene dimethyl acetal to methoxyketene (prepared in situ) using a method established[10,11] for other such substrates, gave only one product, 1,4,4-trimethoxybut-3-en-2-one (**5**), in a 39% yield which could be increased to 56% by using excess ketene acetal (3 equiv) (Scheme I). The enolsilylation of this substance according to Danishefsky and Kitahara[12] as adapted to acylketene acetals[2] gave a 71% yield of the desired diene, 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene as a mixture of the *E* and *Z* isomers (**6a,b**).

The usefulness of this new diene was first tested by reaction with 2-chloro-8-hydroxy-6-methoxynaphthoquinone (**13**) in refluxing benzene followed by pyrolysis and methylation in the usual manner (Scheme III). A 78% yield of 1,2,4,5,7-pentamethoxyanthraquinone (**21**) was obtained, which unfortunately could not be compared with a sample of the substance described earlier. However all physical and spectral characteristics of the two preparations are concordant including the fact that on crystallization from benzene and petroleum ether dimorphous yellow and brown crystals are formed.[13] A second experiment involved a condensation with 6-acetyl-3-chloro-5-methoxy-7-methylnaphthoquinone (**19**)[3] and, in this case, gave an excellent yield of 2-acetyl-5-hydroxyemodin tetramethyl ether (**18**) which up to this point had been difficult to prepare (vide supra). Finally a reaction with 2-bromo-5-chloro-8-methoxy-6-methylnaphthoquinone (**22**) yielded the expected 4-chloro-1,5,6,8-tetramethoxy-3-methylanthraquinone (**24**; 38%) along with 10% of an unexpected product, 4-chloroemodin trimethyl ether (**23**). The formation of this compound requires a reductive elimination of bromine and methoxyl and is analogous to a process known to occur in the presence of ethanol[14] at ~150 °C, a condition which exists during the pyrolytic stage. The chloroanthraquinone (**24**) could then be reduced with hydrazine and palladium[15] to the trimethyl ether of xanthorin (**25**; 29%).

Experimental Section

Melting points were taken for samples in capillary tubes with a Thomas-Hoover apparatus (calibrated thermometer). The IR and UV spectra were determined with Beckman IR-12 and DK-1A spectrophotometers, respectively. The NMR spectra were recorded with Hitachi-Perkin-Elmer R-24A and Bruker HX-90 spectrometers (tetramethysilane as internal standard). The mass spectra were obtained with a Varian M-66 spectrometer. Davison silica gel No. 923 was used for column chromatography, Baker-7G silica gel for preparative TLC, and Woelm silica gel, activity III, for dry column chromatography.

1,4,4-Trichlorobut-3-en-2-one (3). This substance was prepared according to the procedure described for the 4,4-dichloro compound[9] from chloroacetyl chloride (113 g, 1.00 mol), anhydrous aluminium chloride (133 g, 1.00 mol) and 1,1-dichloroethylene (97.0 g, 1.00 mol). Steam distillation and fractionation of the crude product gave the trichlorobutanone **3** (82.0 g, 47%): bp 52–53 °C (0.5 mm Hg); mp 45–48 °C; IR ν_{max} (carbon tetrachloride) 1730 (C=O) and 1600 (C=C) cm^{-1}; NMR δ (60 MHz, $CDCl_3$) 4.05 (2 H, s, 1-H_2) and 6.95 (1 H, s, 3-H). Anal. Calcd for $C_4H_3Cl_3O$: C, 27.70; H, 1.74; Cl, 61.33. Found: C, 27.77; H, 1.76; Cl, 60.99.

1,4,4-Trimethoxybut-3-en-2-one (5). To a mixture of ketene dimethyl acetal[16] (**4**; 16.5 g, 0.188 mol) and triethylamine (7.50 g, 0.0740 mol) in anhydrous ethyl ether (60 mL) was added (1.5 h) under nitrogen a solution of methoxyacetyl chloride (6.80 g, 0.0627 mol) in the same solvent (20 mL). The reaction mixture was stirred for 4 h at room temperature, filtered, and evaporated. Distillation of the residue gave the trimethoxybutenone **5** (5.6 g, 56%): bp 95–103 °C (0.3 mm Hg); mp 46–48 °C; IR ν_{max} (film) 1650 (C=O) and 1600 (C=C) cm^{-1}; NMR δ (60 MHz, $CDCl_3$) 3.48 (3 H, s, 1-OCH_3), 3.83 and 3.95 (6 H, 2s, 4,4-OCH_3), 4.14 (2 H, s, 1-H_2), and 4.93 (1 H, s, 3-H). Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.75; H, 7.28.

(*E*)- and (*Z*)-1,1,4-Trimethoxy-3-trimethylsilyloxybuta-1,3-diene (6a,b). To a solution of 1,4,4-trimethoxybut-3-en-2-one (**5**; 10.3 g, 0.0644 mol) and triethylamine (14.6 g, 0.145 mol) in anhydrous benzene (20 mL) was added (15 min) chlorotrimethylsilane (13.2 g, 0.122 mol). The temperature of the reaction mixture rose slightly and was kept at 40 °C for 3 h. After stirring for 24 h at room temperature, the suspension was filtered and evaporated. The residue upon distillation gave the dienes **6a,b** (10.6 g, 71%): bp 68–76 °C (0.3 mm Hg); IR ν_{max} (film) 1654, 1630 (C=C), and 835 (Si–C str) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 0.19, 0.27, and 0.29 (3s, 3-$OSi(CH_3)_3$), 3.36, 3.52, 3.57, and 3.64 (4s, 1,1,4-OCH_3), 3.78 and 3.91 (2s, 2-H), 4.48 and 5.79 (2s, 4-H). The mixture is very unstable but can be kept for 2 weeks at −20 °C.

1-Butyl-7-chloro-5,8-dihydroxy-2,4-dimethoxyanthraquinone (8). A mixture of 2,6-dichloronaphthazarin[17,18] (**7**; 100 mg, 0.380 mmol), 1,1-dimethoxy-3-trimethylsilyloxyocta-1,3-diene[2] (**1**; 140 mg, 0.390 mmol), and anhydrous benzene (5 mL) was refluxed for 2 h and evaporated to dryness. The residue was heated at 150 °C for 1 h and hydrolyzed by boiling for 30 min in a solution of methanol (5 mL) and 5% hydrochloric acid (3 mL). The crude product, extracted with chloroform was selectively methylated by refluxing for 15 h with dimethyl sulfate (235 mg) and anhydrous potassium carbonate (50 mg) (both added in several portions) in dry acetone (15 mL). Purification by chromatography on silica gel (dry column, chloroform) gave the expected anthraquinone **8** (84 mg, 56%): mp 200–201 °C (acetone); UV λ_{max} (ethanol) 238, 258, 287, 296 sh, 480, and 495 nm (log ϵ 4.58, 4.07, 4.10, 4.04, 4.08, and 4.07); IR ν_{max} (KBr) 1650 and 1625 (chelated C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 0.97 (3 H, ~t, J ~ 6.0 Hz, 4′-H), 1.31–1.64 (4 H, m, 2′,3′-H_2), 3.09 (2 H, ~t, J ~ 6.5 Hz, 1′-H_2), 3.97 and 4.03 (6 H, 2s, 2,4-OCH_3), 6.72 (1 H, br s, 3-H), 7.30 (1 H, s, 6-H), 13.28 and 13.39 (2 H, 2s, 5,8-OH); *m/e* 392/390 (M^+). Anal. Calcd for $C_{20}H_{19}ClO_6$: C, 61.46; H, 4.90; Cl, 9.08. Found: C, 61.73; H, 5.11; Cl, 9.01.

1-Butyl-2,4,5,7,8-pentamethoxyanthraquinone (10). A suspension of 1-butyl-7-chloro-5,8-dihydroxy-2,4-dimethoxyanthraquinone (**8**) (35 mg, 0.0854 mmol), sodium methoxide (1.00 g), copper(I) iodide (35 mg) in anhydrous methanol (5 mL), and dry dimethylformamide (5 mL) was refluxed for 24 h, poured into water, and acidified. Chromatography of the crude product (dry column,

chloroform) gave 1-butyl-5,8-dihydroxy-2,4,7-trimethoxyanthraquinone (**9**; 28 mg). The foregoing material (40 mg) was methylated in the usual way [dimethyl sulfate (200 mg), potassium carbonate (500 mg), and dry acetone (5 mL) for 3 h] and after purification by chromatography (dry column, chloroform) gave the pentamethoxyanthraquinone **10** (21 mg, 50%): mp 166–167 °C (petroleum ether, bp 90–120 °C); UV λ_{max} (ethanol) 227, 262, 288, and 400 nm (log ϵ 4.47, 4.18, 4.16, and 3.86); IR ν_{max} (KBr) 1670 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 0.94 (3 H, ~t, $J \sim 7.0$ Hz, 4′-H_3), 1.22–1.67 (4 H, m, 2′,3′-H_2), 2.91 (2 H, ~t, $J \sim 7.0$ Hz, 1′-H_2), 3.90, 3.92, and 3.96 (2 × 3 H and 1 × 9 H, 3s, 2,4,5,7,8-OCH_3), 6.62 and 6.68 (2 H, 2s, 3,6-H); *m/e* 414 (M^+). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.31; H, 6.51.

1-Butanoyl-2,4,5,7,8-pentamethoxyanthraquinone (11). Oxygen was bubbled into a solution of 1-butyl-2,4,5,7,8-pentamethoxyanthraquinone (**10**; 17 mg, 0.041 mmol) in ethanol (5 mL) which was simultaneously heated under reflux and irradiated with two 375-W floodlamps (2 h). The residue obtained after evaporation of the solvent was chromatographed on silica gel (dry column, chloroform). The product was purified by preparative TLC (chloroform–methanol, 40:1) and gave the acylanthraquinone **11** (4 mg, 22%) (methanol), mp 150–152 °C and 210–211 °C (lit.[5] 152–153.5 °C and 214–215 °C), identical (mmp, TLC in five solvent systems, and IR spectra) with an authenic sample.

2-Chloro-8-hydroxy-6-methoxynaphthoquinone (13). To a suspension of anhydrous aluminium chloride (1.50 g) in redistilled nitrobenzene (6 mL) was added 2-chloro-6,8-dimethoxynaphthoquinone[1] (**12**; 250 mg, 0.990 mmol). The mixture was stirred for 1 h at room temperature then poured into water containing concentrated hydrochloric acid (50 mL) and agitation is continued 15 h. Petroleum ether (bp 65–110 °C) (300 mL) is then added and the heterogenous mixture is filtered. The residue consisted of the expected juglone **13** (215 mg, 91%): mp 177–178 °C (petroleum ether, bp 90–120 °C, benzene); UV λ_{max} (ethanol) 220, 273, 283 sh, and 445 nm (log ϵ 4.59, 4.15, 4.03, and 3.81); IR ν_{max} (KBr) 1670 (C=O) and 1640 (chelated C=O) cm^{-1}; NMR (60 MHz, $CDCl_3$) 3.95 (3 H, s, 6-OCH_3), 6.71 (1 H, d, J = 2.5 Hz, 7-H), 7.19 (1 H, s, 3-H), 7.25 (1 H, d, J = 2.5 Hz, 5-H), and 11.95 (1 H, s, 8-OH); *m/e* 240/238 (M^+). Anal. Calcd for $C_{11}H_7ClO_4$: C, 55.36; H, 2.96; Cl, 14.86. Found: C, 55.59; H, 2.93; Cl, 15.00

2-Acetyl-1,6,8-trimethoxy-3-methylanthraquinone (14). (a) A mixture of 2-chloro-6,8-dimethoxynaphthoquinone (**12**; 100 mg, 0.397 mmol) and 2-acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene[1] (**2**; 220 mg, 1.38 mmol) in xylene (5 mL) was refluxed for 20 h. Purification by column chromatography (chloroform) followed by preparative TLC (benzene–ethyl acetate, 9:1) gave 2-acetylemodin trimethyl ether (**14**; 70 mg, 50%): mp 220–221 °C (methanol); UV λ_{max} (chloroform) 278, 400 nm (log ϵ 4.32, 3.73); IR ν_{max} (KBr) 1710 (hindered CH_3CO–) and 1665 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.34 (3 H, s, 3-CH_3), 2.54 (3 H, s, 2-$COCH_3$), 3.92, 3.96, and 3.98 (9 H, 3 s, 1,6,8-OCH_3), 6.76 (1 H, d, J = 2.5 Hz, 7-H), 7.31 (1 H, d, J = 2.5 Hz, 5-H), and 7.83 (1 H, s, 4-H); *m/e* 354 (M^+). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.92; H, 5.18.

(b) 2-Chloro-8-hydroxy-6-methoxynaphthoquinone (190 mg, 0.797 mmol) and the acetylbutadiene **2** (380 mg, 2.38 mmol) were refluxed in xylene (5 mL) for 8 h. The crude product was separated by chromatography (dry column, chloroform), methylated in the usual way [dimethyl sulfate (500 mg), potassium carbonate (500 mg), and acetone (10 mL) for 8 h], and rechromatographed (benzene–ethyl acetate, 9:1) giving the same anthraquinone **14** (220 mg, 78%).

2-Acetyl-1,6,8-trihydroxy-3-methylanthraquinone (2-Acetylemodin, 15). 2-Acetyl-1,6,8-trimethoxy-3-methylanthraquinone (**14**, 22 mg) was stirred in a mixture of anhydrous aluminium chloride (5.0 g) and sodium chloride (1.0 g) for 5 min at 90 °C. The cooled reaction mixture was hydrolyzed with ice (20 g) and concentrated hydrochloric acid (5 mL) then extracted with ethyl acetate. Purification of the crude product by preparative TLC (chloroform–methanol, 100:1) gave 2-acetylemodin (10 mg, 53%) indistinguishable from a sample of the authentic material (mmp, IR spectra, and TLC in five solvent systems).

2-Acetyl-6-chloro-5,8-dihydroxy-1-methoxy-3-methylanthraquinone (16). A mixture of 2,6-dichloronaphthazarin[17,18] (**7**; 120 mg, 0.463 mmol), 2-acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene (**2**; 220 mg, 1.38 mmol), and 2 mL of xylene was stirred at 115 °C for 4 h, cooled, and chromatographed (dry column, benzene) and gave the chloroanthraquinone **16** (135 mg, 81%): mp 186–188 °C (benzene–petroleum ether, bp 65–110 °C); UV λ_{max} (ethanol) 233, 257 and 475 nm (log ϵ 4.40, 4.39, and 3.96); IR ν_{max} (KBr) 1710 (CH_3CO) and 1640 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.41 (3 H, s, 3-CH_3), 2.58 (3 H, s, 2-$COCH_3$), 3.91 (3 H, s, 1-OCH_3), 7.42 (1 H, s, 7-H), 8.04 (1 H, s, 4-H), 13.03 and 13.28 (2 H, 2s, 5,8-OH); *m/e* 362/360 (M^+). Anal. Calcd for $C_{18}H_{13}ClO_6$: C, 59.93; H, 3.63, Cl, 9.83. Found: C, 59.84; H, 3.39; Cl, 9.52.

2-Acetyl-1,5,6,8-tetramethoxy-3-methylanthraquinone (18). (a) A suspension of 2-acetyl-6-chloro-5,8-dihydroxy-1-methoxy-3-methylanthraquinone (**16**; 100 mg, 0.278 mmol), sodium methoxide (2.35 g, 43.5 mmol), and copper(I) iodide (100 mg, 0.524 mmol) in methanol (10 mL) and dimethylformamide (10 mL) was refluxed for 12 h, poured into ice water, acidified, and extracted with chloroform. The crude product was methylated in the usual way [methyl sulfate (1.50 g in three portions), potassium carbonate (1.50 g), and acetone (20 mL) for 24 h] and by chromatography (dry column, chloroform) gave a mixture of two substances. These were separated on a second column (benzene). A first zone consisted of 2-acetyl-6-chloro-1,5,8-trimethoxy-3-methylanthraquinone (**17**; 16 mg, 15%): mp 198–199 °C (benzene–petroleum ether, bp 90–120 °C); IR ν_{max} (KBr) 1685 (CH_3CO–) and 1670 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.33 (3 H, br s, 3-CH_3), 2.52 (3 H, s, 2-$COCH_3$), 3.91 and 3.98 (3 H and 6 H, 2s, 1,5,8-OCH_3), 7.33 (1 H, s, 7-H), and 7.74 (1 H, br s, 4-H); *m/e* 390/388 (M^+). Anal. Calcd for $C_{20}H_{17}ClO_6$: C, 61.78; H, 4.41; Cl, 9.12. Found: C, 62.22; H, 4.50; Cl, 9.09. A more polar mixture of solvents (benzene–ethyl acetate, 5:1) eluted the desired anthraquinone **18** (14 mg, 13%): mp 154–155 °C (benzene–petroleum ether, bp 90–120 °C); UV λ_{max} (ethanol) 227, 252, 281, and 410 nm (log ϵ 4.41, 4.36, 4.21, and 3.83); IR ν_{max} (KBr) 1700 (CH_3CO–) and 1675 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.33 (3 H, br s, 3-CH_3), 2.53 (3 H, s, 2-$COCH_3$), 3.92, 3.94, and 3.99 (3 H, 3 H, and 6 H, 3s, 1,5,6,8-OCH_3), 6.82 (1 H, s, 7-H) and 7.76 (1 H, br s, 4-H); *m/e* 384 (M^+). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.78; H, 5.26.

(b) A mixture of 7-acetyl-2-chloro-8-methoxy-6-methylnaphthoquinone[1] (**19**; 170 mg, 0.610 mmol), 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene (**6a,b**; 375 mg, 1.62 mmol; added in three portions), and anhydrous benzene (5 mL) was refluxed for 3 h and evaporated to dryness. The residue was heated at 150 °C for 1 h, hydrolyzed by boiling in a solution of methanol (5 mL) and 5% hydrochloric acid (2.5 mL) for 15 min, extracted with chloroform, and methylated in the usual way. The crude product was purified by dry column chromatography (chloroform) and preparative TLC (chloroform) and gave the same anthraquinone **18** (202 mg, 86%). This product was identical (mmp, IR spectra, and TLC in five solvent systems) with the tetramethyl ether obtained in the usual way from a sample of authentic 2-acetyl-5-hydroxyemodin (**20**) (dimethyl sulfate and potassium carbonate in boiling acetone).

1,2,4,5,7-Pentamethoxyanthraquinone (21). By an analogous procedure (compound **13**, method b) using 2-chloro-8-hydroxy-6-methoxynaphthoquinone (**13**; 225 mg, 0.943 mmol) and 1,1,4-trimethoxy-3-trimethylsilyloxybutadiene (**6a,b**; 450 mg, 1.94 mmol) in benzene (5 mL), the pentamethoxyanthraquinone **21** was obtained after pyrolysis, hydrolysis, methylation, and dry column chromatography (benzene–ethyl acetate, 1:1) (273 mg, 78%): mp 189.5–190 °C (benzene–petroleum ether, bp 90–120 °C) (lit.[13] 193 °C); UV λ_{max} (ethanol) 225, 285, and 415 nm (log ϵ 4.59, 4.36, and 3.85); IR ν_{max} (KBr) 1670 and 1655 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 3.92, 3.96, 3.98, and 3.99 (3 H, 6 H, 3 H, 3 H, 4s, 1,2,4,5,7-OCH_3), 6.71 (1 H, d, J = 2.0 Hz, 6-H), 6.79 (1 H, s, 3-H), and 7.22 (1 H, d, J = 2.0 Hz, 8-H); *m/e* 358 (M^+). Anal. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C, 63.74; H, 5.27.

4-Chloro-1,5,6,8-tetramethoxy-3-methylanthraquinone (24). From a similar reaction mixture prepared with 2-bromo-5-chloro-8-methoxy-6-methylnaphthoquinone[19] (**22**; 490 mg, 1.55 mmol) and trimethoxytrimethylsilyloxybutadiene (**6a,b**; 800 mg, 3.44 mmol) in benzene (25 mL, 4 h) was obtained (after pyrolysis, hydrolysis, and methylation) by dry column chromatography (benzene–ethyl acetate, 9:1) a fast moving zone consisting of 4-chloro-1,6,8-trimethoxy-3-methylanthraquinone (**23**; 52 mg, 10%), mp 217–218.5 °C, which was identical in all respects with a sample obtained earlier.[19] Elution with a 1:1 mixture of benzene and ethyl acetate gave the trimethyl ether of chloroxanthorin (**24**; 221 mg, 38%): mp 209.5–210 °C (benzene–petroleum ether, bp 90–120 °C) (lit.[20] mp 210–211 °C); UV λ_{max} (ethanol) 226, 258, and 400 nm (log ϵ 4.52, 4.33, and 3.97); IR ν_{max} (KBr) 1680 and 1670 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.47 (3 H, s, 3-CH_3), 3.94 and 3.97 (2 × 6 H, 2s, 1,5,6,8-OCH_3), 6.71 (1 H, s, 7-H), and 7.07 (1 H, s, 2-H); *m/e* 378 ($M^+ + 2$), 376 (M^+). Anal. Calcd for $C_{19}H_{17}ClO_6$: C, 60.56; H, 4.55; Cl, 9.41. Found: C, 60.99; H, 4.77; Cl, 9.40.

1,3,4,8-Tetramethoxy-6-methylanthraquinone (25). The reductive dehalogenation[15] of 4-chloro-1,5,6,8-tetramethoxy-3-methylanthraquinone (**24**) was carried out by refluxing a mixture of this quinone (76 mg, 0.202 mmol), 100% hydrazine hydrate (83.5 mg, 1.67 mmol; added in three portions of 10.0, 24.5, and 49.0 mg), 10% palladized charcoal (100 mg), and ethanol (13 mL) for 3 h. Chromatog-

raphy of the crude product (dry column, chloroform) gave the expected anthraquinone **25** (20 mg, 29%): mp 185–186 °C (toluene–petroleum ether, bp 90–120 °C) (lit.[21] 185–186 °C;[22] 189–190 °C); UV λ_{max} (chloroform) 280 and 406 nm (log ϵ 3.96 and 3.38); IR ν_{max} (KBr) 1665 (C=O) cm^{-1}; NMR δ (60 MHz, $CDCl_3$) 2.40 (3 H, s, 6-CH_3), 3.90 and 3.95 (3 H and 9 H, 2s, 1,3,4,8-OCH_3), 6.75 (1 H, s, 2-H), 7.00 (1 H, br s, 7-H), and 7.50 (1 H, br s, 5-H); *m/e* 342 (M^+). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.77; H, 5.35. Demethylation of this compound (17 mg) according to Tanaka and Kaneko[21] gave xanthorin (6 mg, 40%), mp 247–248 °C (acetic acid) (lit.[21] 244–246 °C; lit.[22] 253 °C; lit.[23] 250–251 °C) indistinguishable from a sample of the authentic material (mmp, IR spectra, and TLC in four solvent systems).

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Registry No.—**1**, 61539-63-7; **2**, 65120-61-8; **3**, 61501-60-4; **4**, 922-69-0; **5**, 65120-62-9; **6a**, 65120-63-0; **6b**, 65120-64-1; **7**, 13719-93-2; **8**, 65120-65-2; **9**, 65120-66-3; **10**, 65120-67-4; **11**, 65120-68-5; **12**, 57165-99-8; **13**, 65120-69-6; **14**, 65120-70-9; **15**, 32013-63-1; **16**, 65120-71-0; **17**, 65120-72-1; **18**, 65120-73-2; **19**, 65120-74-3; **20**, 32013-66-4; **21**, 1989-44-2; **22**, 52431-64-8; **23**, 52431-72-8; **24**, 37567-67-2; chloroacetyl chloride, 79-04-9; 1,1-dichloroethylene, 75-35-4; methoxyacetyl chloride, 38870-89-2; chlorotrimethylsilane, 75-77-4; xanthorin, 17526-15-7.

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Biosynthesis of α-Naphthocyclinone[1]

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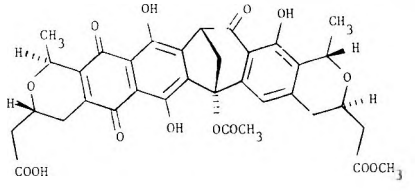
The biosynthesis of α-naphthocyclinone in *Streptomyces arenae* was studied by feeding experiments with sodium [1-^{13}C]- and [2-^{13}C]acetate and diethyl [2-^{13}C]malonate followed by ^{13}C NMR analysis. The compound is derived entirely from acetate/malonate units by the polyketide pathway, and the labeling pattern is consistent with its formation from two benzoisochroman quinone units. Surprisingly, [2-^{13}C]malonate labels both the starter and the chain extension units, but not the acetoxy group. Possible explanations of the latter finding are suggested.

The naphthocyclinones are a series of closely related pigments which were isolated from cultures of *Streptomyces arenae*, strain Tü 495.[2] Some of the compounds, β- and γ-naphthocyclinone (I and II, Scheme I), exhibit antibacterial activity against gram-positive organisms. Their structure elucidation by Zeeck's group showed[2,3] that the naphthocy-

Scheme I. Structures of Naphthocyclinones



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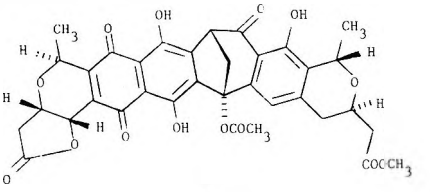
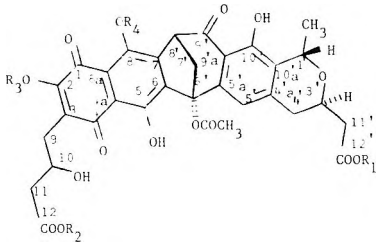


II



III: R_1=CH_3, R_2=R_3=R_4=H, α-naphthocyclinone
IV: R_1=R_2=R_3=R_4=H, α-naphthocyclinone acid
V: R_1=R_2=R_3=CH_3, R_4=H
VI: R_1=R_2=R_3=R_4=CH_3

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Table I. Incorporation of Precursors into α-Naphthocyclinone and α-Naphthocyclinone Acid

Expt no.	Precursor fed	Feeding time after inoculation, h	No. of cultures	Amount fed, mg	Spec. radioactivity of precursor, dpm/mmol	Product isolated (III + IV), mg	Spec. radioactivity of product, dpm/mmol	Incorporation,[a] %	Dilution factor[b]	Relative enrichment per labeled atom[c]
1	Sodium [1-^{14}C]acetate	24	2	50	7.05×10^6	0.1		Not determined		
2	Sodium [1-^{14}C]acetate	32	2	50	7.05×10^6	18.7	1.03×10^6	0.7	6.9	0.9
3	Sodium [1-^{14}C]acetate	40	2	50	7.05×10^6	30.9	1.58×10^6	1.7	4.5	1.4
4	Sodium [1-^{14}C]acetate	48	2	50	7.05×10^6	22.0	2.55×10^6	2.0	2.8	2.3
5	Sodium [1-^{14}C]acetate	48	4	200	2.16×10^7	41.0	8.39×10^6	1.0	2.6	2.4
6	Sodium [1-^{13}C,-1-^{14}C]acetate	48	10	300	1.55×10^7	106	5.9×10^6	1.6	2.6	2.4
7	Sodium [2-^{13}C,-2-^{14}C]acetate	48	10	300	1.51×10^6	98	3.55×10^5	1.0	4.3	1.5
8	Diethyl [2-^{14}C]malonate	48	10	500[d]	1.69×10^7	64.3	4.31×10^5	0.08	39	0.2
9	Diethyl [2-^{14}C]malonate	48	5	250[e]	1.30×10^7	29.6	3.40×10^6	0.5	3.8	1.7
10	Diethyl [2-^{13}C,-2-^{14}C]malonate	48	10	500[e]	2.08×10^7	44.1	3.6×10^6	0.3	5.7	1.2

[a] (Radioactivity in product/radioactivity in precursor) × 100 (%). [b] Specific radioactivity of precursor/specific radioactivity of product. [c] 100/(no. of precursor units in product molecule × dilution factor). [d] Precursor added neat. [e] Precursor fed as solution in Me_2SO.

clinones are related to the general class of isochroman quinone antibiotics, which also includes granaticin,[4,5] frenolicin,[6] kalafungin,[7] actinorhodin,[8] and the nanaomycins[9] and griseusins.[10] The naphthocyclinones are dimers in which one of the naphthoquinone units has been modified to an aryl ketone moiety. Furthermore, in α-naphthocyclinone (III), the major metabolite, the other unit contains only 14 rather than the usual 16 carbon atoms.

In this communication we report some results which establish the biogenetic origin of α-naphthocyclinone.

Results and Discussion

Inspection of the structure of the naphthocyclinones suggests that their biosynthesis might proceed via the polyketide pathway from acetate as the precursor. This hypothesis was examined in a series of feeding experiments with ^{13}C-labeled acetate and malonate followed by determination of the ^{13}C distribution in the resulting α-naphthocyclinone using ^{13}C NMR analysis.

In a series of preliminary experiments, optimum conditions for the ^{13}C experiments were determined. By following the time course of naphthocyclinone formation in *Streptomyces arenase*, strain Tü 495, determined by measuring the absorption at the λ_{max} of α-naphthocyclinone at 488 nm, it was established that the pigment concentration reached a maximum 72 h after inoculation (Figure 1) Chromatography of the pigment mixture showed that α-naphthocyclinone (III) and α-naphthocyclinone acid (IV) were the two most prevalent compounds. Next, a series of experiments with sodium [1-^{14}C]acetate were carried out in which the precursor, in a concentration of 25 mg per flask, was added at different times after inoculation (Table I, expt 1–4). Each set of cultures was harvested 24 h later, and the specific radioactivity and yield of α-naphthocyclinone (III and IV) were determined. It is evident that the best result is obtained when the precursor is added at 48 h. Doubling the amount of precursor per flask (Table I, expt 5) does not give higher isotope enrichment in the product. Based on this exploratory work, feeding at a concentration of 30 mg of sodium acetate per flask at 48 h and

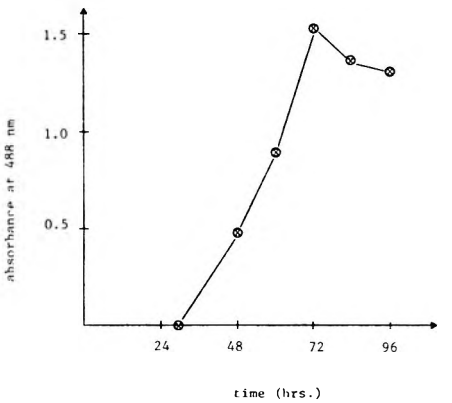


Figure 1. Time course of production of α-naphthocyclinone and α-naphthocyclinone acid.

harvesting at 72 h were chosen as the set of standard conditions for the ^{13}C feeding experiments.

The results of the experiments with sodium [1-^{13}C,1-^{14}C]- and [2-^{13}C,2-^{14}C]acetate are shown in Table I (expt 6 and 7). It is evident that both C-1 and C-2 of acetate are efficiently incorporated. For the analysis of the ^{13}C distribution of the products from these experiments, α-naphthocyclinone and α-naphthocyclinone acid were combined and the mixture was methylated with diazomethane[3] to give α-naphthocyclinone methyl ester methyl ether (V). This compound was subjected to ^{13}C NMR spectroscopy, and the normalized peak heights of the spectra were compared to those of the natural abundance spectrum. A complete ^{13}C NMR analysis of V and other naphthocyclinones has been carried out in Zeeck's laboratory, and the signal assignments were made available to us.[11] The relative ^{13}C abundance values for the products of experiments 6 and 7 (Table II) show that all carbon atoms of α-naphthocyclinone, with the exception of the *O*-methyl group, originate from acetate and that C-1 and C-2 of acetate label the molecule in the alternating pattern predicted by the polyketide pathway. This same kind of labeling pattern has

Table II. ^{13}C Distribution in the α-Naphthocyclinone Ring System Biosynthesized from [^{13}C]Acetate and [^{13}C]Malonate

Carbon atom no.	α-Naphthocyclinone methyl ester methyl ether (V)			α-Naphthocyclinone methyl ester dimethyl ether (VI)	
	Chemical shift, ppm	^{13}C abundance[a] from: [1-^{13}C]acetate	[2-^{13}C]acetate	Chemical shift, ppm	^{13}C abundance[a] from diethyl [2-^{13}C]malonate
1	183.5	4.0	1.1	178.9	1.3
2	158.9	1.2	2.6	159.9	2.5
3	131.8	4.4	1.2		
4	188.7	1.2	2.8	190.9	2.8
4a	111.9	3.5	1.2		
5	152.3	1.2	2.8	153.0	3.0
6	146.1	4.3	1.2		
7	134.8	1.0	2.6	122.6[b]	2.6
8	154.6	4.3	1.1	151.0	1.2
8a	112.3	1.2	2.8		
9	30.0	1.2	2.6	29.6	3.1
10	66.9	4.2	1.3	66.9	1.1
11	40.9	1.0	3.0	40.8	2.6
12	172.5	4.4	1.2	172.5	1.0
1′	67.9	3.9	1.1	67.9	1.1
3′	63.2	3.5	1.3	63.2	1.2
4′	34.5	1.0	2.6	34.5	2.6
4′a	142.1	4.1	1.2	142.3	1.1
5′	113.1	1.2	3.3	113.0	3.1
5′a	140.2	4.1	1.2	140.6	1.5
6′	84.8	1.1	2.8	84.7	2.9
7′	49.5	4.0	1.1	49.5	1.1
8′	51.0	1.2	2.4	51.9	2.5
9′	198.6	3.7	1.0	199.5	1.2
9′a	107.9	1.0	2.5	108.0	3.0
10′	159.6	4.0	1.1	159.5	1.1
10′a	128.8	1.0	2.3	128.6	3.0
11′	40.6	1.2	2.6	40.5	2.6
12′	171.1	4.2	1.2	171.1	0.9
1′-CH_3	18.6	1.1	2.6	18.6	2.8
Acetyl CO	169.5	4.3	1.0	169.3	1.1
Acetyl CH_3	21.1	1.1	2.3	21.1	1.3
Ester OCH_3	51.6	1.2	1.2	51.6	1.3
2-OCH_3	61.8[c]	1.1	1.1	61.3[c]	1.1
8-OCH_3				62.2	1.1

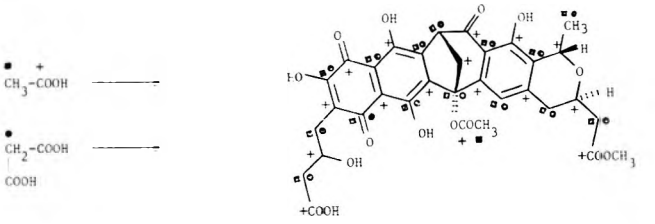
[a] Natural abundance = 1.1; values are subject to an error of approximately ±15%. [b] Tentative assignment. [c] Reference signal used for normalization of peak heights.

been demonstrated for the simpler benzoisochroman quinones, nanaomycin A and B.[12]

Since the "left hand" half of α-naphthocyclinone contains only a 14-carbon skeleton, it could either have arisen from a 16-carbon unit by loss of the two carbon atoms representing the starter unit of the polyketide chain or it could represent a 14-carbon polyketide chain with either C-2 and C-1 or C-4 and C-4a as the starter unit. We attempted to distinguish between these possibilities by feeding [2-^{13}C]malonate, which we expected to label predominantly the chain extension units and not, or only to a lesser extent, the starter units. Since malonic acid or its salt frequently cannot penetrate the cell membrane, the diethyl ester was administered to the culures.[13] The results (Table II) surprisingly indicate that with the exception of the *O*-acetyl group the same carbon atoms were labeled by [2-^{13}C]malonate as by [2-^{13}C]acetate. Derivatization of the sample from this experiment accidentally gave a new compound instead of V, to which structure VI was tentatively assigned, although an alternative structure carrying the extra methyl group at C-5 cannot be excluded. Only partial ^{13}C NMR assignments could be made for this compound, but the signals for the critical carbon atoms 2 and 4 and for the methyl group at C-1′ were assigned unambiguously. As would be predicted if the starter unit from the left hand portion of the molecule is lost, both C-2 and C-4 are enriched. However, any conclusion to that effect is invalidated by the fact that the C-1′ methyl group is enriched to the same extent. Paradoxically, the methyl group of the acetoxy function is not enriched.

The results clearly show that the skeleton of α-naphthocyclinone is built up entirely from acetate and/or malonate units via the polyketide pathway (Scheme II). In agreement with the proposal of Zeeck et al.,[2] we believe that the biosynthesis of α-naphthocyclinone involves the dimerization of two 16-carbon polyketides followed by loss of a 2-carbon unit from one of them. However, experimental verification of this hypothesis is still lacking. At least two reasonable explanations can be offered for the finding that malonate labels both the starter unit and the chain extension units, but not the acetoxy group. Malonyl-CoA may serve both as starter and as chain

Scheme II. Labeling Pattern of α-Naphthocyclinone from [^{13}C]Acetate and [^{13}C]Malonate



extension unit, with the starter unit undergoing decarboxylation at a subsequent stage. Alternatively, assembly of the polyketide chain may occur much earlier in the fermentation period than O-acetylation, and acetyl-CoA and malonyl-CoA may be in rapid equilibrium, resulting in labeling of both pools at the time of polyketide assembly, whereas the added precursor may be largely consumed at the time O-acetylation occurs. Further experimentation will be necessary to clarify these and other details of this biosynthesis.

Experimental Section

General. NMR spectra were measured on a JEOL PFT-100 system interfaced to an EC-100 Fourier transform computer with 20K memory. ^{13}C NMR spectra were generally recorded at a pulse width of 20 μs and a repetition time of 5 s using $CDCl_3$ as solvent. IR spectra were obtained on a Beckman IR 4230 spectrometer and UV spectra on a Perkin-Elmer 124 or a Cary 17 instrument. Mass spectra were measured on a DuPont 21-492 BR mass spectrometer.

Analytical as well as preparative chromatographic separations were carried out on thin-layer plates or columns of oxalic acid treated silica gel prepared as described by Zeeck and Mardin.[3] Radioactivity determinations were made by liquid scintillation counting in a Beckman LS-250 spectrometer using Bray's solution[14] as the scintillation fluid. Counting efficiences were determined with [^{14}C]toluene as an internal standard. ^{14}C-Labeled compounds were purchased from Amersham-Searle and ^{13}C-labeled substrates from Merck Sharp and Dohme.

Culture Conditions. *Streptomyces arenae*, strain Tü 495, was maintained on slants of M2 agar (1% malt extract, Difco, 0.4% dextrose, 0.4% yeast extract, Difco). Production cultures of 100 mL of medium (2% soy flour, 2% mannitol, pH 7.2) in 500-mL baffled Erlenmeyer flasks were inoculated with 2 × 2 cm pieces of mycelium cut from agar slants and were incubated at 27 °C and 350 rpm on a rotary shaker. The time course of the fermentation was determined by inoculating a series of four cultures and removing 2-mL aliquots from each flask at 24, 30, 48, 56, 72, 83, and 95 h after inoculation. These samples were each shaken with 2 mL of ethyl acetate, and the absorbance of the ethyl acetate solution at 488 nm was determined after appropriate dilution. The points shown in Figure 1 are the averages of the four determinations.

Labeled precursors were added as sterile aqueous solutions (except in expts 8–10) at the times and in the amounts indicated in Table I, and the cultures were harvested 24 h later. In all ^{13}C experiments the precursor was mixed with a small amount of ^{14}C-labeled material to allow determination of the overall dilution factor.

Isolation and Purification of Products. At the end of the fermentation period the mycelium was separated from the culture medium by filtration with the aid of Celite. The damp mycelium was extracted with acetone, the extract was concentrated in a vacuum, and the resulting aqueous suspension was combined with the culture filtrate. The mixture was acidified to pH 3 with 1 N HCl and extracted with ethyl acetate. The extract was dried and evaporated to dryness; the residue was taken up in a small volume of ethyl acetate, and the crude pigment mixture was precipitated out with petroleum ether and collected by centrifugation. This material was then chromatographed on a column (1.8 × 24 cm) of 30 g of oxalic acid treated silica gel. Elution with chloroform/ethyl acetate (1:1) gave α-naphthocyclinone and α-naphthocyclinone acid (IV), in addition to traces of other pigments which were not collected. The α-naphthocyclinone and α-naphthocyclinone acid were combined and suspended in chloroform. A solution of diazomethane in ether was added dropwise at −20 °C until a clear red solution was obtained and no more starting material was detectable by TLC analysis (acetone/chloroform, 1:9; oxalic acid treated silica gel). The solvent was evaporated, and the residue was chromatographed on a column (1.8 × 48 cm) of 60 g of oxalic acid treated silica gel. Elution with chloroform containg 2% acetone gave α-naphthocyclinone methyl ester methyl ether (V). In the feeding experiment with diethyl [2-^{13}C]malonate, α-naphthocyclinone acid was formed almost exclusively and the diazomethane methylation was carried out on a solution of this material (44.1 mg) in 30 mL of chloroform/methanol (2:1). Workup as above gave a new derivative (37 mg) which was tentatively identified as α-naphthocyclinone methyl ester dimethyl ether (VI). The material was identical to the product from the methylation of V.

α-Naphthocyclinone Methyl Ester Dimethyl Ether. α-Naphthocyclinone methyl ester methyl ether[3] (213 mg) was dissolved in 50 mL of chloroform/methanol (1:1), and excess diazomethane solution in ether was added at room temperature. The solution was evaporated to dryness, and the residue was chromatographed on 100 g of oxalic acid treated silica gel (chloroform containing 2% acetone) to give 149 mg of product, which was recrystallized from carbon tetrachloride/cyclohexane (2:3), mp 116 °C; IR (KBr) 1738, 1670, 1637 sh, 1623, 1579 cm^{-1}; UV (EtOH) λ_{max} 427 nm (ε 4300), 332 (5900), 247 sh, 228 (44 500); UV (EtOH/NaOH) λ_{max} 555 nm (ε 5400), 378 (12 100), 276 sh, 232 (44 500); UV ($CHCl_3$) λ_{max} 438 nm (ε 3400), 328 (5300), 286 sh, 249 sh, end absorption; ^1H NMR ($CDCl_3$) δ 12.74 (5-OH), 11.98 (10′-OH), 6.97 (5′-H), 5.00 (1′-H), 4.35 (3′-H), ca. 4.2 (10-H), 4.12 (2-OCH_3), 3.88 (8-OCH_3), ca. 3.8 (7′-H_a), 3.73 (12′-OCH_3), 3.69 (12-OCH_3), 2.93 (7′-H_b), 2.4–3.0 (4 CH_2 groups), 2.29 (6′-$OCOCH_3$), 1.52 (1′-CH_3).

Molecular weight for $C_{36}H_{36}O_{15}$: calcd, 708.204; observed (by EI mass spectrometry), 708.219.

Acknowledgment. We are greatly indebted to Dr. Axel Zeeck of the University of Göttingen for providing *Streptomyces arenae* Tü 495, reference samples of the naphthocyclinones, and the ^{13}C NMR assignments for these compounds.

Registry No.—I, 55050-83-4; II, 55095-58-4; III, 54826-93-6; IV, 54367-38-3; V, 54367-41-8; VI, 65015-70-5; sodium acetate, 127-09-3; diethyl malonate, 105-53-3.

References and Notes

(1) This work was supported by U.S. Public Health Service Research Grant AI 11728 from the National Institute for Allery and Infectious Diseases and by a Postdoctoral Fellowship (to K.S.) from the Max-Kade Foundation, New York.
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Marine Natural Products. Synthesis of Four Naturally Occurring 20β-H Cholanic Acid Derivatives[1a]

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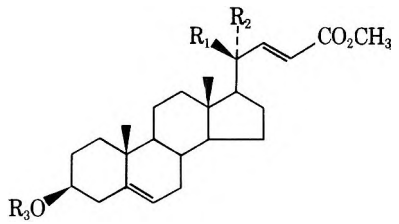
Received August 2, 1977

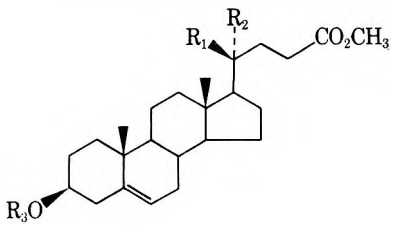
In conjunction with the structural elucidation of novel steroids from the marine invertebrate *Ptilosarcus gurneyi* (sea pen) we required the synthesis of a series of cholanic acid derivatives in which both epimers at C(20) were elaborated. The synthesis of the 20β-H compounds (20-epi) 1–4 provides convincing evidence that the naturally occurring marine steroids contain the unexpected "unnatural" stereochemistry at C(20). In addition to establishing the structures of the natural products, a comparison of the physical and spectral data revealed that the 20β-H (20-epi) compounds consistently differed from their 20α-H counterparts in two respects: (1) exhibit significantly shorter gas chromatographic retention times; and (2) display the C(21) methyl resonance at ~0.1 ppm higher field in the NMR spectra than the 20α-H compounds. These differences are consistent with conformational isomerism of the side chain as a result of the chirality at C(20).

The number of novel sterols from marine sources[2] is increasing dramatically due to new and more discriminating chromatographic and spectral techniques as well as a greater appreciation of older methods.[3] In addition to novel structures, marine species have recently been shown to contain very complex mixtures of sterols.[3,4] While the variety and complexity of marine sterols is being demonstrated, a recent computer-assisted analysis,[5] utilizing only known biosynthetic processes and oxygenation at C(3), has suggested the possibility of a tenfold increase in anticipated new sterols.

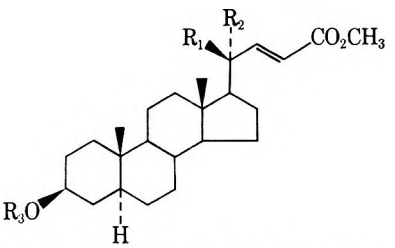
As part of this search for sterols and other biologically important compounds from marine sources we earlier reported[6] the isolation of six novel steroids (chromatographically distinct from the free sterols) from a sea pen, *Ptilosarcus gurneyi*. We concluded from spectral evidence and synthesis that the major component of the steroid mixture[7] was methyl (*E*)-3β-acetoxy-$\Delta^{5,22}$-choladienate (1) with the unexpected 20*S* stereochemistry. Since our earlier preliminary report,[6] we have completed the synthesis of **2, 3,** and **4** and conclude, based on the data presented herewith, that these are the correct structures of three additional components of the marine steroid mixture.[7] In the present paper, we wish to report the details of the syntheses of **1–4**. Additionally, we present data in agreement with the implication of side-chain conformational isomerization[8] as a consequence of the chirality at C(20).



1, $R_1 = CH_3$; $R_2 = H$; $R_3 = Ac$
16, $R_1 = H$; $R_2 = CH_3$; $R_3 = Ac$



2, $R_1 = CH_3$; $R_2 = H$; $R_3 = Ac$
17, $R_1 = H$; $R_2 = CH_3$; $R_3 = Ac$



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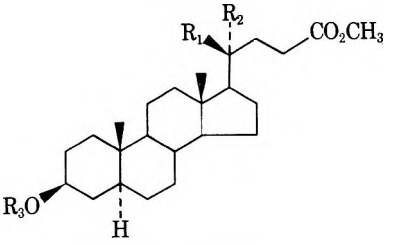

4, $R_1 = CH_3$; $R_2 = H$; $R_3 = Ac$
18, $R_1 = H$; $R_2 = CH_3$; $R_3 = Ac$

Results and Discussion

Our approach to the synthesis of the 20β-H steroids was (1) to proceed via an intermediate in which the stereochemistry at C(20) could easily be changed, (2) to separate the pure epimeric intermediates, and (3) to elaborate a desired side chain. The known isomethyl ether aldehyde **5**, readily available[9–12] from stigmasterol, seemed a good choice in that the C(20) carbon is epimerizable and the aldehyde functionality could be utilized with a variety of reagents to elaborate a desired side chain. Realizing the difficulties[9] attendant with the separation of the epimeric aldehydes, we chose to carry out the purification at the level of the isomeric alcohols **6** and **7** which could then be reconverted to the corresponding aldehydes.

Epimerization of the aldehyde **5** with 5% methanolic KOH followed by lithium aluminum hydride ($LiAlH_4$) reduction yielded the desired alcohols **6** and **7** accompanied by two additional alcohols (Scheme I). The two unexpected alcohols were shown to be the C(20) epimeric pregnane derivatives **8** and **9**, whose acid hydrolysis[13] products **10** (R = H) and **11** (R = H) and corresponding acetates (**10** and **11**, R = Ac) were compared with authentic samples[14] prepared from pregnenolone. The formation of the 20-hydroxy pregnane side chain from **5** is believed to proceed via the mechanism outlined in Scheme II by analogy to that reported for 1-phenyl-2-indanone.[15] Generation of the C_2 side chain (i.e., 6β-methoxy-3α,5-cyclo-5α-pregnan-2-one before $LiAlH_4$ reduction) is a slow process under the reaction conditions employed, resulting in a 35% yield of the alcohols **8** and **9** after 60 h. Verification that **8** and **9** arise via the mechanism outlined in Scheme II and

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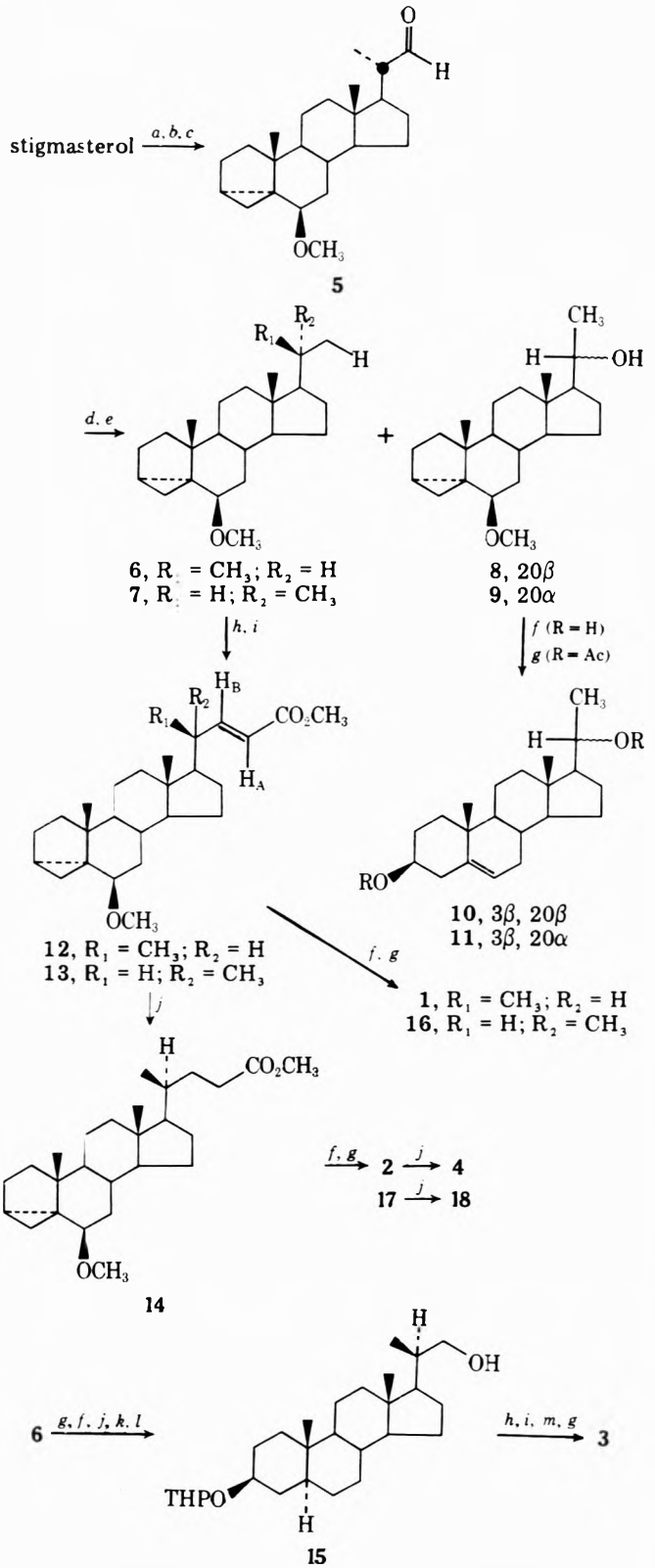
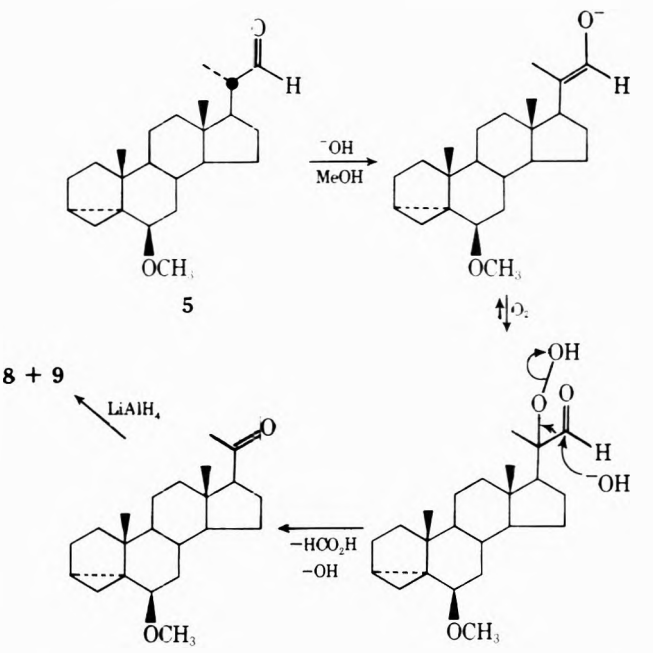
Scheme I



Scheme II



[a] TsCl/pyr. [b] KOAc/MeOH. [c] O_3/CH_2Cl_2, −78 °C. [d] 5% KOH/MeOH, room temp, 58 h. [e] $LiAlH_4/Et_2O$, 0 °C. [f] p-TsOH/p-dioxane–H_2O (8:2). [g] Ac_2O/pyr. [h] CrO_3 2pyr/CH_2Cl_2, room temp, 15 min. [i] $Ph_3P{=}CHCO_2CH_3$/glyme, room temp, 17 days. [j] H_2/PtO_2. [k] Dihydropyran, $POCl_3$, 4 h. [l] 5% KOH/MeOH, reflux, 2 h. [m] THF–AcOH–H_2O (3:2:1), 12 h.

further studies relating to the preparative utility of this side-chain degradation are presently under investigation.

In spite of this unforeseen event, the four alcohols **6–9** were readily purified by thin-layer mesh silica gel column chromatography. For regeneration of the desired side chain, the alcohols **6** and **7** were oxidized in essentially quantitative yield under mild conditions with Collin's reagent[16] to their corresponding aldehydes followed by condensation of the aldehydes with the Wittig reagent carbomethoxymethylenetriphenylphosphorane[17] to yield **12** and **13**. Gas chromatographic (GC) and ^1H NMR analysis of **12** and **13** (see Table I and Experimental Section) showed that only one product was produced in each case,[18] indicating that the oxidation and Wittig reactions proceeded without affecting the stereochemistry at C(20). Acidic hydrolysis[13] of the isomethyl ether functionality of **12** and **13** and acetylation (Ac_2O/pyr) yielded the desired 20*S* (**1**) and 20*R* (**16**) epimers of methyl (*E*)-3β-acetoxy-$\Delta^{5,22}$-choladienate. The required methyl (20*S*)-3β-acetoxy-Δ^5-cholenate (**2**) was prepared by hydrogenation of **12** to yield **14** followed by hydrolysis of the isomethyl ether protecting group and acetylation. To obtain methyl (*E*,20*S*)-3β-acetoxy-Δ^{22}-5α-cholenate (**3**), the alcohol **6** was converted to the tetrahydropyranyl ether **15** in five straightforward steps (see Scheme I). Oxidation of **15** to the corresponding aldehyde, condensation with the Wittig reagent in the same manner as before, followed by conversion of the tetrahydropyranyl ether protecting group to the acetate yielded **3**. The completely saturated methyl (20*S*)-3β-acetoxy-5α-cholanate (**4**) was obtained by catalytic hydrogenation of **2**.

The "natural" 20*R* (20α-H) analogue of **2**, methyl 3β-acetoxy-Δ^5-cholenate (**17**), is commercially available and upon catalytic hydrogenation provided the known methyl 3β-acetoxy-5α-cholanate (**18**).[19]

Table I contains the gas chromatographic and ^1H NMR data for the compounds prepared above. The GC, ^1H NMR, and mass spectral data of compounds **1–4** and **16–18** were compared with the GC–MS data of the sea pen steroid mixture (R_3 = Ac).[6,7] As reported earlier,[6] the "unnatural" (20*S*)-dienate **1** (*m/e* 428) was identical in all respects with the major component of the marine steroid mixture. From the data presented in Table I we conclude that structures **2**, **3**, and **4** correspond to three additional minor components. Our stereochemical assignments are rendered unambiguous, since Table I further shows that the 20β-H (20*S*) and 20α-H (20*R*) compounds differ markedly in two respects. First the 20β-H compounds display consistently a greater gas chromatographic mobility; furthermore, the C(21) methyl group of the 20β-H compounds is shifted ~0.1 ppm upfield in the NMR spectrum

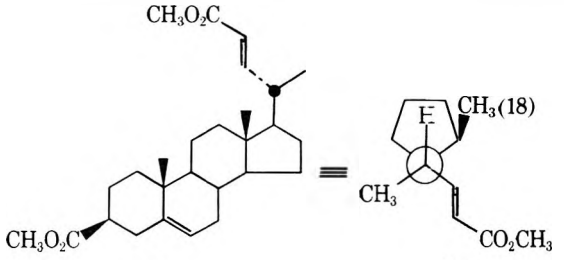
Table I. Gas Chromatographic and ^{1}H NMR Data of Various 20-Epi Steroid Pairs

Compd	C(23)H_A[b]	C(22)H_B[b]	C(18)[b]	C(19)[b]	C(21)[b]	$-CO_2CH_3$[b]	Retention time, min
2			0.70	1.03	0.04	3.68	12.7
17			0.69	1.03	0.94	3.68	13.9
peak A[a]							12.7
4			0.68	0.83	0.83	3.68	12.7
18			0.66	0.82	0.92	3.68	13.9
peak A							12.7
1	5.78	6.91	0.66	1.00	1.00	3.74	13.9
16	5.74	6.87	0.74	1.03	1.10	3.72	16.6
peak B[a]							13.9
428 component	5.78	6.91	0.65	0.99	0.99	3.74	
430 component	5.76	6.89	0.62	0.80	0.99	3.74	
3	5.76	6.89	0.62	0.80	0.98	3.73	13.9
12	5.77	6.91	0.69	1.01	0.99	3.73	7.4
13	5.73	6.84	0.75	1.02	1.08	3.71	9.8
6			0.72	1.00	0.93		3.4
7			0.73	1.01	1.03		3.8
20-isocholesterol[8a]			0.69	1.03	0.81		6.3
cholesterol[8a]			0.69	1.02	0.91		6.9

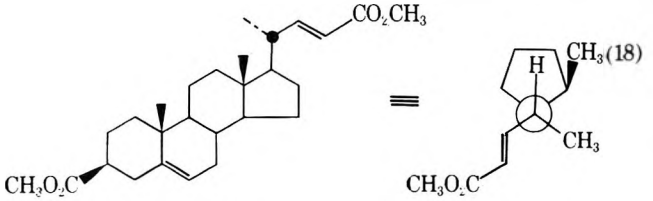
[a] See Experimental Section. [b] In parts per million (δ).

relative to the 20α-H counterparts. Similar effects have been observed in studies of the C(20) epimeric 11-oxygenated cholesterols,[20] 20-hydroxyprogesterones,[21] 20-hydroxycholesterols,[22] $\Delta^{17(20)}$-cholesterols,[22] and 25-oxo-25-norcholesterols.[23]

The ^{1}H NMR and gas chromatographic data for the 20β-H compounds can be rationalized in terms of the side chain existing preferentially in that conformer wherein the C(21) methyl group resides in the shielding anisotropy cone of the C(16)–C(17) bond and the remainder of the side chain projects to the left (cis relative to C(13)) as depicted in **19**. An argument



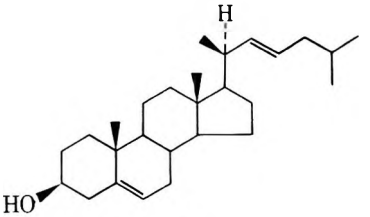
1 **19**



16 **20**

against a preferred conformer in 20β-H sterols has recently been raised by Trachtenberg et al.,[24] who maintain that there exists only a small barrier to rotation around the C(17)–C(20) bond equalizing the ground-state conformer populations. While our NMR data are incapable of settling this question, we feel that sterols, epimeric at C(20) but of identical conformer composition, should exhibiy identical gas chromatographic behavior which is contrary to our present observations.

While the C(21) ^{1}H NMR data may be a more consistent parameter of the C(20) stereochemistry, the gas chromatographic mobility may be the more useful criterion in future analyses of naturally occurring sterol mixtures, especially in the event of very small quantities. The large gas chromatographic difference of 3.5 min between the C(20) epimers **1** and **16** is probably a maximum value due to the rigidity of the side chain imposed by the (*E*)-Δ^{22} bond and the polar group at the side-chain terminus. The still observable difference for **6** and **7** (as well as the moderate value for cholesterol and 20-isocholesterol) suggests that for side chains of C_4 and longer one may be able to assign the C(20) stereochemistry solely on the basis of gas chromatographic mobility. While this possibility needs to be fully tested, Idler et al.[25] have assigned the C(20) chirality as *S* for a marine sterol (isolated from a scallop) which exhibited an unusually short retention time in the GC–MS analysis and whose mass spectrum was consistent with a cholesta-5,22-dien-3β-ol (**21**) structure.



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We have analyzed our sea pen's free sterols by procedures recently published;[3] our results are in agreement with the analysis conducted nine years earlier by Ciereszko et al.[26] The free sterols possess the "normal" C(20) stereochemistry by comparison of the GC rentention times with those of cholesterol, 20-isocholesterol, and the extensively studied *P. porosa* sterols.[3] The sea pen sterol mixture was similar to that obtained from several sponges collected from the northern California waters,[27] suggesting that these sterols may arise from exogenous sources and that they are not the immediate biosynthetic precursors of the 20-epi steroids **1–4**. Whether the 20-epi steroids arise from an exogenous source (either directly or biosynthesized from an exogenous sterol) or are the result of in vivo biosynthesis by the sea pen is a matter we hope to answer later through radioactive labeling experiments.

Experimental Section

General. Low-resolution mass spectra were obtained on an AEI MS-9 spectrometer, operated by Mr. R. Ross. Combined GC–MS analysis was performed using a Hewlett Packard 7610A gas chromatograph equipped with 2-mm i.d. × 10 ft "U"-shaped column (3% OV-17 at 260 °C) and interfaced with a Varian Mat 711 double-focusing mass spectrometer (equipped with an all glass Watson–Biemann dual stage separator and a PDP-11/45 computer for data acquisition and reduction), operated by Annemarie Wegmann.

The 60-MHz nuclear magnetic resonance (NMR) spectra were run on a Varian Associates T-60 NMR spectrometer, and the 100-MHz spectra were run on a Varian Associates HA-100 NMR instrument by Dr. L. Durham. All NMR spectra were taken in $CDCl_3$ solution with Me_4Si as internal reference unless otherwise specified. Infrared (IR) spectra were obtained on a Perkin-Elmer 700 infrared spectrophotometer and ultraviolet spectra (UV) were obtained on a Cary 14 recording spectrophotometer in EtOH. Rotations were measured on a Perkin-Elmer 141 polarimeter.

Gas chromatography of all steroids was performed on a U-shaped glass column, packed with 1% OV-25 on 100–200 mesh Gas-Chrom Q. This column was mounted in a Hewlett-Packard 402 high-efficiency gas chromatograph with a hydrogen flame detector. All injections were made with the column temperature at 252 °C and the flash heater and the detection temperatures at 270 °C with the He flow at 75 mL/min.

Thin-layer chromatography was carried out on plates 5 × 20 cm coated with 250 μm of silica gel PF 254. The melting points (uncorrected) were determined on a Thomas-Hoover "Uni-Melt" capillary melting point apparatus.

Microanalyses were performed in the Microanalytical Laboratory, Department of Chemistry, Stanford University, by Mr. E. Meier and associates.

Isolation of Steroid Mixture. Five specimens of *Ptilosarcus gurneyi* were collected on August 6, 1974 off Sand City Beach, Calif., by dredging at ~30 ft. The freshly collected specimens weighed 600 g which reduced to 69 g after drying at <50 °C. The dried sea pens were extracted twice with hexane at room temperature to yield 4.2 g of extract. The entire hexane extract was dissolved in benzene and chromatographed on 100 g of Florisil (60–100 mesh). A 1-L benzene fraction yielded 652 mg of high molecular weight steryl esters. A subsequent 1-L ethyl acetate fraction yielded 984 mg of the sterols and more polar compounds. Rechromatography of the 984-mg sample on 125 g of silica gel (60–230 mesh) utilizing 10% EtOAc/benzene as eluting solvent yielded 343 mg of sterols (R_f identical with cholesterol and stigmasterol) in fractions 48–54. Fractions 67–78 were combined to yield 21.8 mg of a more polar compound which was UV-visible and stained the same red color as the less polar sterols when sprayed with 10% $Ce(SO_4)_2/H_2SO_4$ spray reagent. Acetylation (Ac_2O/pyr) of the material in fractions 67–78 and subsequent chromatography on thin-layer mesh silica gel yielded 10 mg of an acetylated product homogenous by TLC.

Gas chromatography of this acetylated material showed three peaks, labeled A, B, and C, with relative composition 20, 80, and <1%, respectively. The NMR (60 MHz) spectrum of this mixture displayed singlet signals at δ 3.70 ($-CO_2CH_3$) and 3.61 ($-CO_2CH_3$) in a relative ratio of 4:1. The ultraviolet spectrum (UV) exhibited a maximum at λ 215 nm (ϵ_{max} ~7000, EtOH) and the infrared spectrum (IR) had a strong absorption at 1710 cm^{-1}.

Combined GC–MS indicated peaks A, B, and C were composed of two components each. GC–MS of peak A: *m/e* 432 and 430 (1:9);[28] (70 eV) *m/e* (rel intensity) M^+ 432 (3), no parent for 430 observed, 372 (19, $M^+ - 60$), 370 (100, base peak $M^+ - 60$), 357 (4), 355 (15), 277 (2), 275 (3), 257 (3), 255 (10), 249 (18), 217 (5), 215 (10), 213 (9), 175 (5), 173 (5), 135 (17), 133 (10), 131 (8), 121 (13), 119 (12), 107 (18), 105 (15), 95 (18), 93 (14), 91 (17), 83 (13), 81 (27), 71 (11), 69 (19), 67 (15), 57 (21), 55 (32). GC–MS of peak B: *m/e* 430 and 428 (3:7);[28] (70 eV) *m/e* (rel intensity) M^+ 430 (3), no parent for 428 observed, 415 (1), 384 (8), 382 (16), 370 (38, $M^+ - 60$), 368 (100, base peak $M^+ - 60$), 355 (8), 353 (10), 257 (34), 255 (8), 230 (6), 228 (5), 215 (19), 213 (10), 201 (11), 199 (6), 187 (12), 175 (12), 175 (8), 173 (10), 161 (25), 159 (20), 157 (9), 147 (39), 145 (27), 143 (9), 135 (20), 133 (25), 131 (14), 121 (27), 119 (23), 117 (9), 115 (9), 114 (55), 109 (21), 107 (43), 105 (32), 95 (33), 93 (35), 91 (30), 83 (11), 81 (52), 79 (29), 69 (17), 67 (28), 57 (12), 55 (36). GC–MS of peak C: *m/e* 444 and 442 (1:1);[28] mass spectrum was very weak, only three discernable peaks *m/e* 384 ($M^+ - 60$), 382 ($M^+ - 60$), 269.

One milligram of the peak B compounds was obtained by preparative GC on a 3% OV-17 column. The NMR (100 MHz) spectral data are presented listing the signals of the major component first: *m/e* 428 component δ 6.91 (1 H, dd, *J* = 16 and 9.5 Hz, $-CHCH{=}CHCO_2CH_3$), 5.78 (1 H, d, *J* = 16 Hz, $-CHCH{=}CHCO_2CH_3$), 5.36 (1 H, br t, C(6) olefinic proton), 4.65 (1 H, m, C(3)α proton), 3.74 (3 H, s, $-CO_2CH_3$), 2.03 (3 H, s, CH_3CO_2-), 0.99 (3 H, d, *J* = 6.5 Hz, C(21)), 0.99 (3 H, s, C(19)), 0.65 (3 H, s, C(18)); *m/e* 430 component δ 6.89 (1 H, dd, *J* = 16 and 9 Hz, $-CHCH{=}CHCO_2CH_3$), 5.76 (1 H, d, *J* = 16 Hz, $-CHCH{=}CHCO_2CH_3$), 3.74 (3 H, s, $-CO_2CH_3$), 2.02 (3 H, s, CH_3CO_2-), 0.99 (3 H, d, *J* = 6.0 Hz, C(21)), 0.80 (3 H, s, C(19)), 0.62 (3 H, s, C(18)).

(20*R*)-20-Hydroxymethyl-6β-methoxy-3α,5-cyclo-5α-pregnane (6) and (20*S*)-20-Hydroxymethyl-6β-methoxy-3α,5-cyclo-5α-pregnane (7). The freshly prepared isomethyl ether aldehyde **5** (2.025 g, 6.12 mmol) was dissolved in 50 mL of 5% KOH/MeOH and stirred at room temperature for 60 h. Periodic GC analysis displayed a gradual increase of a more mobile component which was ~34% of the reaction mixture at workup. The reaction was worked up by removal of most of the MeOH under reduced pressure, water was added, and the aqueous layer was extracted thoroughly with Et_2O. The Et_2O extracts were combined, washed with H_2O, and dried (anhydrous Na_2SO_4) and the solvent was removed to yield 1.04 g (3.14 mmol) of a slightly yellow oil. The aqueous layer was acidified with concentrated HCl to adjust the pH to 7 then to 4. At each pH, the aqueous layer was thoroughly extracted with Et_2O. The Et_2O extracts were treated in a similar fashion as above to yield 465 and 202 mg of material, respectively. The structures of the compounds obtained in the last two Et_2O extracts (primarily two compounds from NMR spectra) were not pursued further. The oily residue from the first Et_2O extract was dissolved in 30 mL of dry Et_2O and added dropwise over a 0.5-h period to a solution of 180 mg (3.1 mmol) of lithium aluminum hydride ($LiAlH_4$) in 30 mL of dry Et_2O at 0 °C. The ice bath was removed and stirring was continued at room temperature for an additional hour. The excess $LiAlH_4$ was destroyed by dropwise addition of saturated aqueous Na_2SO_4 solution. The clear dry Et_2O solution was filtered from the insoluble aluminum salts and Na_2SO_4 and removed under reduced pressure to yield 931 mg of a clear oily residue. TLC and GC of this residue indicated a mixture of four compounds. This mixture was chromatographed on 60 g of thin-layer mesh silica gel employing 10% EtOAc/hexane as solvent and collecting 15-mL fractions. Fractions 26–30 yielded 67.3 mg of pure **8**, fractions 35–43 gave 109 mg of pure **6** (homogenous by TLC and GC), fractions 53–55 provided 51.7 mg of pure **7**, and fraction 73 contained 5.2 mg of pure **9**.

Pure **8** had: P_f 0.43 (20% EtOAc/hexane); NMR (100 MHz) δ 3.70 (1 H, m, C(20β)H), 3.31 (3 H, s, $-OCH_3$), 2.77 (1 H, br t, *J* = 3 Hz, C(6) α proton), 1.12 (3 H, d, *J* = 6.0 Hz, C(21)), 1.02 (3 H, s, C(19)), 0.79 (3 H, s, C(18)), 0.70–0.3 (5 H, m, cyclopropyl); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 332 (54), 317 (53), 300 (76), 277 (100, base peak).

Pure **6** was obtained as a glass and had: R_f 0.35 (20% EtOAc/hexane); $[\alpha]_D$ +41.8° (*c* 2.65, $CHCl_3$); NMR (100 MHz) δ 3.60 (2 H, m, $-CH_2OH$), 3.30 (3 H, s, $-OCH_3$), 2.77 (1 H, br t, *J* = 3 Hz, C(6) α proton), 1.00 (3 H, s, C(19)), 0.93 (3 H, d, *J* = 6.0 Hz, C(21)), 0.72 (3 H, s, C(18)), 0.7–0.3 (3 H, m cyclopropyl); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 346 (48), 331 (53), 314 (65), 291 (100, base peak).

Anal. Calcd for $C_{23}H_{38}O_2$: 346.28527. Found: 346.28336.

Pure **7** was obtained initially as a viscous liquid which solidified on standing. A poorly crystalline solid was obtained from hexane: mp 84.5–86 °C; R_f 0.28 (20% EtOAc/hexane); $[\alpha]_D$ +51° (*c* 0.36, $CHCl_3$) [lit.[10a] $[\alpha]_D$ +47.8° (*c* 0.96, $CHCl_3$)]; NMR (100 MHz) δ 3.50 (2 H, m, $-CH_2OH$), 3.30 (3 H, s, $-OCH_3$), 2.77 (1 H, br t, *J* = 3 Hz, C(6) α proton), 1.03 (3 H, d, *J* = 6.0 Hz, C(21)), 1.01 (3 H, s, C(19)), 0.73 (3 H, s, C(18)), 0.7–0.3 (3 H, m, cyclopropyl); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 346 (57), 331 (54), 314 (72), 291 (100, base peak).

Anal. Calcd. for $C_{23}H_{38}O_2$: 346.2852. Found: 346.28383.

Pure **9** had: R_f 0.25 (20% EtOAc/hexane); NMR (100 MHz) δ 3.70 (1 H, m, C(20β)H), 3.31 (3 H, s, $-OCH_3$), 2.77 (1 H, br t, *J* = 3 Hz, C(6) α proton), 1.21 (3 H, d, *J* = 6.0 Hz, C(21)), 1.01 (3 H, s, C(19)), 0.70 (3 H, s, C(18)), 0.7–0.3 (3 H, m, cyclopropyl).

Compounds **7** and **9** could be more effectively separated by rechromatography on TLC-mesh silica gel employing 30% Et_2O/hexane as solvent.

Methyl (20*S*, 22*E*)-6β-Methoxy-3α,5-cyclo-5α-chol-22-enate (12). To 75 mL of dry CH_2Cl_2 (freshly distilled from P_2O_5) was added 2.40 mL (30.12 mmol) of dry pyridine (distilled from BaO and stored over 4-Å molecular sieves) and 1.50 g (15.06 mmol) of CrO_3. A deep burgundy solution ensued immediately to which was added in one portion 0.87 g (2.51 mmol) of **6** in 10 mL of dry CH_2Cl_2, whereby a tarry black precipitate appeared. The reaction mixture was stirred at room temperature for 15 min, the solution was decanted from the tarry black precipitate, and the latter was washed twice with Et_2O. The CH_2Cl_2/Et_2O solution was removed under reduced pressure at < 35 °C to yield an oily residue. TLC and GC analysis of the oily residue showed the complete disappearance of **6** and indicated the presence of a new compound (more mobile on TLC and GC) whose R_f and GC retention time closely matched that for **5**. Since all indications pointed to the formation of the aldehyde (20*R*), the oily residue was dissolved in 75 mL of glyme (freshly distilled from $LiAlH_4$) to which was added 5 g (15 mmol) of $Ph_3P{=}CHCO_2CH_3$. The reaction was stirred at room temperature for 17 days under an argon atmosphere. The glyme was then removed under reduced pressure to yield

a solid residue which was partitioned between hexane and 75% MeOH/H_2O. The aqueous MeOH layer was thoroughly extracted with hexane, the hexane layers were combined and dried (anhydrous Na_2SO_4), and the hexane was removed under reduced pressure to yield 660 mg of the crude oily product. Chromatography on silica gel yielded 510 mg of pure **12** as a viscous liquid, homogeneous by GC and TLC.

Pure **12** had: NMR (100 MHz) δ 6.91 (1 H, dd, J = 16 and 9.5 Hz, -CHCH=$CHCO_2CH_3$), 5.77 (1, H, d, J = 16 Hz, -CHCH=$CHCO_2CH_3$), 3.73 (3 H, s, $-CO_2CH_3$), 3.32 (3 H, $-OCH_3$), 2.77 (1 H, br t, J = 3 Hz, C(6) α proton), 1.01 (3 H, s, C(19)), 0.99 (3 H, d, J = 6 Hz, C(21)), 0.69 (3 H, s, C(18)), 0.7–0.3 (m, cyclopropyl); mass spectrum (70 eV) M^+ 400 (43), 385 (53), 368 (69), 345 (100, base peak).

Methyl (20*R*,22*E*)-6β-Methoxy-3α,5-cyclo-5α-chol-22-enate (13). In a similar fashion to that described above, 42 mg (0.12 mmol) of **7** was oxidized and immediately reacted with Ph_3P=$CHCO_2CH_3$ in glyme. Workup of the Wittig reaction after 3 days resulted in only a 50% yield (TLC, GC, and NMR) of the α,β-unsaturated ester **13.** The unreacted aldehyde was found to be inseparable from **13** on silica gel and was therefore removed by treatment with $NaBH_4$ in MeOH at 0 °C. Subsequent silica gel column chromatography yielded 13.2 mg of pure **13**, homogeneous by TLC and GC.

Pure **13** had: NMR (100 MHz) δ 6.84 (1 H, dd, J = 16 and 9.5 Hz, -CHCH=$CHCO_2CH_3$), 5.73 (1 H, d, J = 16 Hz, -CHCH=$CHCO_2CH_3$), 3.71 (3 H, s, $-CO_2CH_3$), 3.32 (3 H, s, $-OCH_3$), 2.76 (1 H, br t, J = 3 Hz, C(6) α proton), 1.08 (3 H, d, J = 6 Hz, C(21)), 1.02 (3 H, s, C(19)), 0.75 (3 H, s, C(18)), 0.7–0.3 (3 H, m, cyclopropyl); mass spectrum (70 eV) m/e (rel intensity) M^+ 400 (47), 385 (51), 368 (68), 345 (100, base peak).

Methyl (20*S*,22*E*)-3β-Acetoxychola-5,22-dienate (1). To a solution of 508 mg of **12** in 50 mL of p-dioxane and 20 mL of H_2O was added ~50 mg of p-TsOH. The reaction mixture was heated to reflux for 0.5 h, cooled to room temperature, and analyzed by GC. The GC analysis indicated quantitative hydrolysis to the 3β-hydroxy-Δ^5 functionality. At the addition of 30 mL of H_2O a white solid precipitated which was collected on a filter. The NMR (60 MHz) was consistent with the expected product. The white solid (97.4 mg) was dissolved in 5 mL of Ac_2O and 5 mL of pyridine and allowed to stand overnight. The excess of Ac_2O and pyridine were removed in vacuo to yield 95.4 mg of a slightly yellow solid. Recrystallization from MeOH yielded pure **1** as long needles: mp 151–151.5 °C.

Pure **1** had: $[\alpha]_D$ −85° (c 0.14, $CHCl_3$); UV λ_{max} 218 nm (ϵ_{max} 13 000); NMR (100 MHz) 6.91 (1 H, dd, J = 16 and 9.5 Hz, -CHCH=$CHCO_2CH_3$), 5.87 (1 H, d, J = 16 Hz, -CHCH=$CHCO_2CH_3$), 5.38 (1 H, m, C(6) olefinic proton), 4.60 (1 H, m, CH_3CO_2CH–), 3.74 (3 H, s, $-CO_2CH_3$), 2.04 (3 H, s, CH_3CO_2–), 1.00 (3 H, s, C(19)), 1.00 (3 H, d, J = 6 Hz, (C(21)), 0.65 (3 H, s, C(18)); mass spectrum (70 eV) m/e (rel intensity) no parent ion observed, 397 (1), 369 (29), 368 (100, base peak), 353 (9), 255 (9), 215 (2), 213 (7), 199 (3), 197 (2), 187 (6), 185 (2), 173 (4), 171 (3), 161 (9), 159 (12), 157 (5), 147 (19), 145 (17), 143 (8), 133 (15), 131 (9), 121 (15), 119 (12), 114 (8), 107 (20), 105 (19). 93 (17), 91 (15), 81 (24), 79 (14), 67 (12), 55 (12), 43 (22), 41 (9).

Anal. Calcd for $C_{27}H_{43}O_4$: C, 75.66; H, 9.41; mol wt M^+ − 60, 368.26961. Found: C, 75.26; H, 9.37; mol wt (mass spectrum), 368.26770.

The GC retention time of **1** was identical with peak B of the steroid mixture (R_3 = Ac).

Methyl (20*R*,22*E*)-3β-Acetoxychola-5,22-dienate (16). Acidic hydrolysis[13] and acetylation of **13** as described previously yielded 5.4 mg of **16.** Recrystallization from MeOH gave pure **16:** mp 151.5–152 °C; $[\alpha]_D$ −54.3° (c 0.09, $CHCl_3$); UV λ_{max} 210 nm (ϵ_{max} 16 100); NMR (100 MHz) δ 6.87 (1 H, dd, J = 16 and 9.5 Hz, -CHCH=$CHCO_2CH_3$), 5.76 (1 H, d, J = 16 Hz, -CHCH=$CHCO_2CH_3$), 5.36 (1 H, m, C(6) olefinic proton), 4.63 (1 H, m, CH_3CO_2CH–), 3.74 (3 H, s, $-CO_2CH_3$), 2.03 (3 H, s, CH_3CO_2–), 1.08 (3 H, d, C(21)), 1.01 (3 H, s, C(19)), 0.74 (3 H, s, C(18)); mass spectrum (70 eV) m/e (rel intensity) no parent ion observed, 397 (1), 369 (29), 368 (100, base peak), 353 (7), 255 (10), 215 (2), 213 (7), 199 (3), 197 (2), 187 (5), 185 (2), 173 (4), 171 (3), 161 (8), 159 (11), 157 (5), 147 (18), 146 (16), 143 (6), 133 (14), 131 (8), 121 (14), 119 (10), 114 (8), 107 (19), 105 (17), 93 (15), 91 (13), 81 (23), 79 (12), 67 (11), 55 (12), 43 (19), 41 (8).

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41; mol wt M^+ − 60, 368.26961. Found: C, 75.28, H, 9.36; mol wt (mass spectrum), 368.26815.

The GC retention time of **16** was 2.4 min longer than that of **1** and peak B.

Methyl (20*S*)-3β-Acetoxychol-5-enate (2). To a solution of 160 mg of **12** in 30 mL of EtOAc was added a small amount (~5 mg) of PtO_2. The contents of the reaction flask was placed in a hydrogen atmosphere (at a slight positive pressure) overnight. The solution was filtered from the catalyst and the solvent was removed to yield an oily product. The NMR (60 MHz) spectrum indicated complete reduction of the double bond. The oily product was dissolved in 10 mL of p-dioxane and 3 mL of H_2O to which was added 15 mg of p-TsOH followed by heating to reflux for 15 min. The reaction flask was cooled to room temperature and GC analysis indicated quantitative solvolysis of the isomethyl ether functionality. The reaction was worked up as before to yield 113.4 mg of a white solid. This solid was dissolved in 2 mL of Ac_2O and 2.0 mL of pyridine and allowed to stand overnight. The excess Ac_2O and pyridine were removed in vacuo to yield 115 mg of a slightly yellow solid. Recrystallization from MeOH yielded pure **2** as rosettes of needles: mp 119–120 °C.

Pure **2** had $[\alpha]_D$ −54 ± 3° (c 0.9, $CHCl_3$); NMR (100 MHz) 5.39 (1 H, m, C(6) olefinic proton), 4.60 (1 H, m, CH_3CO_2CH–), 3.68 (3 H, s, $-CO_2CH_3$), 2.04 (3 H, s, CH_3CO_2–), 1.03 (3 H, s, C(19)), 0.84 (3 H, d, J = 6 Hz, C(21)), 0.70 (3 H, s, C(18)); mass spectrum (70 eV) m/e (rel intensity) no parent ion observed, 371 (29), 370 (100, base peak), 355 (16), 339 (5), 262 (10), 255 (15), 249 (27), 213 (14), 161 (12), 160 (11), 159 (14), 145 (35), 143 (26), 141 (11), 135 (10), 133 (15), 131 (11), 121 (18), 120 (16), 119 (15), 109 (11), 107 (26), 105 (23), 95 (18), 93 (21), 91 (17), 81 (29), 79 (14) 67 (17), 55 (24), 43 (23), 41 (11).

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.26; H, 9.89.

The GC retention time of **2** was identical with that of peak A of the steroid mixture (R_3 = Ac).

Methyl (20*R*)-3β-Acetoxychol-5-enate (17). Purchased from Steraloids and was not purified further: mp 159–161 °C, $[\alpha]_D$ −45.2° (c 0.55, $CHCl_3$) [lit.[19] $[\alpha]_D$ −45°]; NMR (100 MHz) δ 5.40 (1 H, m, C(6) olefinic proton), 4.60 (1 H, m, CH_3CO_2CH–), 3.68 (3 H, s, $-CO_2CH_3$), 2.04 (3 H, s, CH_3CO_2–), 1.03 (3 H, s, C(19)), 0.94 (3 H, d, J = 6.0 Hz, C(21)), 0.69 (3 H, s, C(18)); mass spectrum (70 eV) m/e (rel intensity) no parent ion observed, 371 (29), 370 (100, base peak), 355 (15), 339 (6), 262 (9), 255 (14), 249 (27), 213 (15), 161 (13), 160 (11), 159 (14), 147 (39), 145 (29), 143 (12), 135 (11), 133 (17), 131 (12), 121 (19), 120 (17), 119 (15), 109 (12), 107 (29), 105 (25), 95 (20), 93 (23), 91 (18), 81 (32), 79 (16), 67 (18), 55 (26), 43 (28), 41 (14).

The GC retention time of **17** was 1.2 min longer than that of **2** and peak A.

Methyl (20*S*)-3β-Acetoxy-5α-cholanate (4). To a solution of 66.2 mg of **2** in 30 mL of EtOAc was added a small amount (~5 mg) of PtO_2. The vigorously stirred solution was placed in a hydrogen atmosphere (at a slight positive pressure) for 8 h. The solution was filtered from the catalyst and removed under reduced pressure to yield 65 mg of a white solid product. Recrystallization from MeOH yielded pure **4:** mp 136–137.5 °C; $[\alpha]_D$ +6.4° (c 0.125, $CHCl_3$); NMR (100 MHz) δ 4.68 (1 H, m, CH_3CO_2CH–), 3.68 (3 H, s, $-CO_2CH_3$), 2.03 (3 H, s, CH_3CO_2–), 0.83 (3 H, s, C(19)), 0.83 (3 H, d, J = 6.0 Hz, C(21)), 0.68 (3 H, s, C(18)); mass spectrum (70 eV) m/e (rel intensity) M^+ 432 (11), 417 (1), 372 (97), 357 (24), 290 (20), 276 (13), 275 (19), 264 (9), 257 (5), 249 (3), 230 (35), 217 (26), 216 (40), 215 (100, base peak), 201 (16), 161 (13), 159 (10), 154 (10), 149 (18), 147 (49), 145 (20), 135 (18), 133 (17), 123 (19), 121 (29), 119 (23), 109 (25), 107 (43), 105 (25), 95 (43), 93 (39), 91 (20), 81 (51), 79 (27), 69 (18), 67 (32), 55 (42), 43 (44), 41 (21).

Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 75.06; H, 10.26.

The GC retention time of **4** was identical with that of peak A of the steroid mixture (R_3 = Ac).

Methyl (20*R*)-3β-Acetoxy-5α-cholanate (18). To a solution of 38 mg of **17** in 20 mL of EtOAc was added a small amount (~5 mg) of PtO_2. The vigorously stirred solution was placed in a hydrogen atmosphere (at a slight positive pressure) for 5.5 h. The solution was filtered from the catalyst and the solvent was removed under reduced pressure to yield 37.2 mg of a white solid product. Recrystallization from MeOH yielded pure **18** as rosettes of needles: mp 159–160 °C (lit.[19] mp 155 °C); $[\alpha]_D$ +9.1° (c 0.66, $CHCl_3$) (lit.[19] $[\alpha]_D$ +11.0°); NMR (100 MHz) δ 4.68 (1 H, m, CH_3CO_2CH–), 3.68 (3 H, s, $-CO_2CH_3$) 2.03 (3 H, s, CH_3CO_2–), 0.92 (3 H, d, J = 6.0 Hz, C(21)), 0.82 (3 H, s, C(19)), 0.66 (3 H, s, C(18)).

The GC retention time of **18** was 1.2 min longer than that of **4** and peak A.

Methyl (20*S*,22*E*)-3β-acetoxy-5α-chol-22-enate (3). A solution of 566.2 mg (1.64 mmol) of **6** in 6 mL of acetic anhydride/6 mL of pyridine was allowed to stand at room temperature overnight. The excess acetic anhydride and pyridine were then removed in vacuo to yield a slightly yellow solid product. TLC and the ^1H NMR spectrum (60 MHz) indicated quantitative acetylation of the C(22) hydroxy group.

To a solution of the crude acetate dissolved in 50 mL of p-dioxane/20 mL of H_2O was added 50 mg of p-toluenesulfonic acid mono-

hydrate. This solution was refluxed for 15 min then cooled to room temperature. GC analysis of the reaction solution indicated complete hydrolysis of the isomethyl ether group to the 3β-hydroxy-Δ^5 functionality. Addition of 50 mL of H_2O yielded a white precipitate which was collected by suction filtration and dried. The ^1H NMR (60 MHz) spectrum was in excellent agreement with the expected structure: NMR (60 MHz) 5.23 (1 H, m, C(6) olefinic proton), 4.17 (1 H, dd, J = 7 and 4 Hz, $-CHCH_3CHHOAc$), 3.82 (1 H, d, J = 7 Hz, $-CHCH_3CHHOAc$), 3.52 (1 H, m, HOCH–), 2.00 (3 H, s, $-CH_2O-COCH_3$), 0.98 (3 H, s, C(19)), 0.90 (3 H, d, J = 6.0 Hz, C(21)), 0.70 (3 H, s, C(18)).

The crude 22-acetoxy-3β-hydroxy-Δ^5 compound was hydrogenated in ethyl acetate solution with PtO_2 in the usual manner and the crude product (no olefinic ^1H NMR signals) was dissolved in 55 mL of dihydropyran containing 150 μL of $POCl_3$. After 3 h at room temperature the reaction mixture was poured onto an equal volume of 10% Na_2CO_3 solution, extracted with ether, washed with water, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to yield the 3β-tetrahydropranyl ether as a clear colorless liquid.

The crude oily liquid was dissolved in 75 mL of 5% KOH/MeOH and heated at reflux for 1 h. Isolation in the usual fashion yielded 530 mg of a slightly yellow solid, which provided pure **15** after recrystallization from MeOH: mp 154.5–157 °C; $[\alpha]_D$ +32 ± 1° (c 1.94, $CHCl_3$); NMR (60 MHz) 4.75 (1 H, m, ROCHR'OR''), 4.07–3.10 (5 H, m, protons α to oxygen atoms), 0.95 (3 H, d, J = 6.0 Hz, C(21)), 0.80 (3 H, s, C(19)), 0.67 (3 H, s, C(18)); mass spectrum (70 eV) m/e (rel intensity) M^+ 418 (2), 317 (53), 299 (24), 85 (100, base peak).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 77.46; H, 11.08. Found: C, 77.20; H, 11.20.

The α,β-unsaturated methyl ester side chain was introduced into **15** (100 mg, 0.2 mmol) as described previously (i.e., **1** and **16**). As in the case of **16** the Wittig reaction was worked up after 3 days resulting in 50.3 mg (45% yield) of the desired product whose NMR (60 MHz) spectrum displayed signals at 6.83 (1 H, dd, J = 16 and 9.5 Hz, $-CHCH{=}CHCO_2CH_3$), 5.68 (1 H, d, J = 16 Hz, $-CHCH{=}CHCO_2CH_3$), 3.67 (3 H, s, $-CO_2CH_3$), 0.98 (3 H, d, J = 6.0 Hz, C(21)), 0.79 (3 H, s, C(18)), 0.66 (3 H, s, C(18)). Without further purification, the THP protecting group of the crude ester was hydrolyzed in 50 mL of THF–AcOH–H_2O (3:2:1) at 40 °C overnight. Subsequent chromatography over thin-layer mesh silica gel resulted in 36.2 mg of a solid, homogeneous by TLC and GC, whose NMR spectrum (60 MHz) was in accord with the expected *trans*-Δ^{22}-3β-hydroxy-5α product. Acetylation (Ac_2O/pyr) yielded 35 mg of **3**, which was recrystallized from MeOH to give long needles: mp 122–123 °C; $[\alpha]_D$ 18 ± 3° (c 0.57, $CHCl_3$); UV λ_{max} 219 nm (ϵ_{max} 6500); NMR (100 MHz) δ 6.89 (1 H, dd, J = 16 and 9.5 Hz, $-CHCH{=}CHCO_2CH_3$), 5.76 (1 H, d, J = 16 Hz, $-CHCH{=}CHCO_2CH_2$), 4.66 (1 H, m, CH_3CO_2CH–), 3.73 (3 H, s, $-CO_2CH_3$), 2.02 (3 H, s, CH_3CO_2–), 0.98 (3 H, d, J = 6.0 Hz, C(21)), 0.80 (3 H, s, C(19)), 0.62 (3 H, s, C(18)); mass spectrum (70 eV) m/e (rel intensity) M^+ 430 (6), 415 (2), 370 (34), 257 (72), 215 (33), 201 (10), 175 (8), 163 (9), 161 (22), 149 (20), 147 (34), 135 (17), 133 (16), 123 (11), 121 (24), 119 (16), 114 (100, base peak), 109 (20), 107 (53), 105 (20), 95 (34), 93 (38), 91 (18), 81 (53), 79 (26), 69 (10), 67 (27), 55 (25), 43 (33), 41 (16).

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.18; H, 9.89.

Preparation of 3β,20β-Diacetoxypregn-5-ene (10) from 8. To a solution of 42 mg of **8** in 5 mL of *p*-dioxane/2 mL of H_2O was added 5 mg of *p*-toluenesulfonic acid monhydrate. The reaction mixture was refluxed for 30 min. Precipitation with H_2O, filtration, and recrystallization from MeOH provided 3β,20β-dihydroxypregn-5-ene (**11**, R = H): mp 200–205.5 °C (lit.[14a] 200–201.5 °C). Acetylation yielded the corresponding diacetate (R = Ac): mp 128.5–131 °C; $[\alpha]_D$ −34 ± 3° (c 0.35, $CHCl_3$) [lit.[14c] mp 130–131 °C; $[\alpha]_D$ −36 ± 1° (c 0.94, $CHCl_3$)].

The ^1H NMR spectrum of **10** (R = Ac) derived from **8** was identical in all respects with that obtained for **10** derived from pregnenolone. The TLC and R_f of **8** and **10** (R = H or Ac) were identical from both sources. No depression in the melting point was observed upon admixture of the two samples, mp 128.5–131 °C.

Preparation of 3β,20α-Diacetoxypregn-5-ene (11) from 9. Identical treatment of **9** yielded the 20α-epimer **11** (R = H), mp 177–179 °C (lit.[14a] 177–178 °C), and upon acetylation the corresponding diacetate **11** (R = Ac): mp 145–148 °C; $[\alpha]_D$ −51.4° (c 2.58, $CHCl_3$) (lit.[14c] mp 145.5–146.5 °C; $[\alpha]_D$ −53.8°). The ^1H NMR spectrum of **11** (R = Ac) derived from **9** was identical in all respects with that obtained for **11** (R = Ac) derived from pregnenolone. The TLC and R_f for **9** and **11** (R = H and Ac) were identical from both sources. An admixture of **11** (R = Ac) from **9** and pregnenolone gave an undepressed melting point: mp 144–147 °C.

Sea Pen Free Sterols. A 300-mg sample of the free sterols obtained in fractions 48–54 from the original sea pen isolation was chromatographed according to published procedures[3] on alumina (90 g, activity III). A small amount of nonsteroid material eluted from the column with 3% Et_2O/hexane. The 5% Et_2O/hexane fractions yielded three trace sterols with molecular ions at m/e 372, 382, and 384. The precise nature of these sterols is as yet unknown, but the presence of fragmentation at m/e 283 [$M^+ - (H_2O$ + side chain)] in the mass spectrum of the m/e 372 sterol and fragments at m/e 269 and 271 [$M^+ - (H_2O$ + side chain)] in the spectra of the m/e 382 and 384 sterols suggest a 4,4-dimethyl structure for the former and a 4-methyl structure for the latter two compounds. Further elution of the column with 8% Et_2O/hexane yielded virtually all of the material applied to the column for which GC–MS data indicated a mixture of seven sterols whose mass spectra exhibited molecular ions at m/e 370, 384, 386, 398, 400, 412, and 414. Mass spectral fragmentation patterns and GC retention times relative to authentic samples of cholesterol, stigmasterol, and the *P. porosa* sterols[3] identified the above seven sterols as 24-norcholesta-5, 22-dien-3-ol, 22,23-dehydrocholesterol, cholesterol, brassicasterol, campesterol, stigmasterol, and sitosterol. The GC retention times further indicated that none of the "free" sterols had the 20-iso stereochemistry. The "free" sterols found here and their relative ratios are essentially the same as those reported earlier.[26]

Registry No.—**1**, 63814-49-3; **2**, 63814-50-6; **3**, 65166-02-1; **4**, 1178-02-5; **5**, 25819-77-6; (20*R*)-**5**, 64783-80-8; **6**, 65166-03-2; **7**, 51231-23-3; **8**, 65166-04-3; **9**, 65166-05-4; **10** (R = H), 901-57-5; **10** (R = Ac), 1913-46-8; **11** (R = H), 901-56-4; **11** (R = Ac), 1913-47-9; **12**, 65166-06-5; **13**, 56259-12-2; **14**, 65166-07-6; **15**, 65120-89-0; **16**, 63780-65-4; **17**, 31823-53-7; **18**, 1255-52-3; $Ph_3P{=}CHCO_2CH_3$, 2605-67-6; (20*S*)-3β-hydroxy-20-acetoxymethylpregn-5-ene, 65120-90-3; dihydropyran, 110-87-2; methyl (20*S*,22*E*)-3β-tetrahydropyranyloxy-22β-dehydro-5α-20-cholanate, 65120-91-4; methyl (20*S*,22*E*)-3β-hydroxy-22-dihydro-5α,20-cholanate, 65166-08-7; methyl (20*S*,23*E*)-3β-hydroxy-5,6,22,23-didehydro-20-cholanate, 63780-68-7; methyl (20*S*)-3β-hydroxy-20-cholanate, 63865-06-5; (21*S*)-3α,5α-cyclo-6β-methoxy-21-acetoxymethylpregnane, 53139-47-2.

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Synthesis of *dl*-Gabaculine Utilizing Direct Allylic Amination as the Key Step

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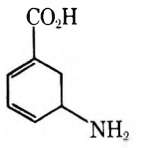
Racemic gabaculine (2,3-dihydro-*m*-anthranilic acid) was synthesized from 3-cyclohexene-1-carboxylic acid in 23% overall yield (seven steps). The key reaction was a direct allylic amination of the *tert*-butyl 3-cyclohexene-1-carboxylate using bis(*N*-*p*-toluenesulfonyl)sulfodiimide. The positional selectivity could be influenced by steric factors with the *N,N*-dicyclohexylamine derivative giving amination almost exclusively in the 5 position. The effect of N-substitution on the electrochemical cleavage of allylic *p*-toluenesulfonamide compounds was investigated. While *N*-alkyl groups had little effect, *N*-acyl groups lowered the reduction potential by as much as 0.3 V.

An important aspect of the chemistry of sulfur(IV) and selenium(IV) imido compounds is the allylic amination of alkenes by bis(*N*-*p*-toluenesulfonyl)sulfodiimide[1,2] and bis(*N*-*p*-toluenesulfonyl)selenodiimide.[3] These reagents directly introduce a nitrogen, protected as the *N*-*p*-toluenesulfonyl derivative, in an allylic position. In the past, the strategies used to create this type of functionality have relied on indirect, multistep operations. In view of the potential scope of this new reaction, it was decided to apply the allylic amination sequence to a total synthesis in order to demonstrate its overall utility.

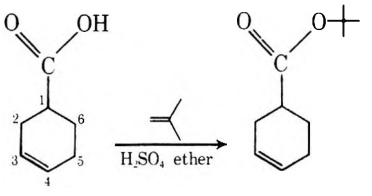
Gabaculine (**1**) was first isolated from a culture filtrate of *Streptomyces toyocaenis* subspecies 1039 by Mishima and co-workers in 1976.[4] It was an optically active amorphous powder and was assigned the structure **1** on the basis of



1

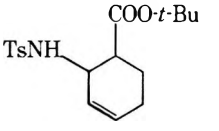
physical and chemical data. This structure was confirmed by the total synthesis of the racemic compound (seven steps from methyl 2,5-dihydrobenzoate, approximately 20% overall yield).[4] Gabaculine is a subject of current biochemical interest since it is an inhibitor of γ-aminobutyrate aminotransferase.[4] This enzyme,[5,6] a member of the general class of aminotransferases,[7] is directly involved in the metabolism of γ-aminobutyric acid (GABA), an important inhibitory transmitter substance in the nervous system.[8,9] Recently, **1** was shown to be a specific irreversible inhibitor of γ-aminobutyrate aminotransferase.[10]

The allylic amine moiety in gabaculine (**1**) was an obvious attraction for us since it suggested that **1** might be easily constructed by a route involving direct allylic amination of a suitable cyclohexenyl precursor. According to this plan, our synthesis begins with 3-cyclohexene-1-carboxylic acid (**2**). Acid **2** is commercially available and contains the complete carbon skeleton of gabaculine. It has two different allylic positions (carbons 2 and 5), but only amination at the 5 position will lead to **1**. It was felt that the positional selectivity could be controlled by esterification of the acid with a large, bulky group. Hopefully, this would disfavor the approach of the reagent toward the 2 position. Preliminary experiments involving the allylic amination reaction were carried out using the *tert*-butyl ester **3**,[11] synthesized in 79% yield by the reaction of **2** with isobutylene under acidic conditions.

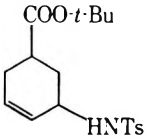


2 **3**

When **3** was added to a solution of TsN=S=NTs in CH_2Cl_2 at 25 °C,[1] a slow reaction took place (5 days). Workup using K_2CO_3 in aqueous MeOH afforded a white solid in yields ranging from 50% to 70%. Although homogeneous by TLC, NMR spectra of this crude product showed two multiplets (δ 3.9 and 4.1 in the ratio of 3:1) in the region where allylic hydrogens α to a *p*-toluenesulfonamido group are observed, as well as resonances due to two different tosyl groups in the aromatic region (δ 7.2–7.9). The minor isomer (δ 4.1, mp 120–121 °C) was isolated by repeated careful fractional recrystallization from $CHCl_3$/hexanes. In the same manner, the major isomer (δ 3.9, mp 83–84 °C) was isolated from the mother liquors. The minor isomer was assigned the structure **4** since irradation of the olefinic protons (in the presence of



4



5

0.1 N $NaOD/D_2O$) caused collapse of the δ 4.1 multiplet to a doublet (J = 3.4 Hz). The major isomer was assigned the structure **5**. The analogous reaction using TsN=Se=NTs[3] also gave a mixture of **4** and **5** (45% yield) in the ratio of 1:1 (by NMR).

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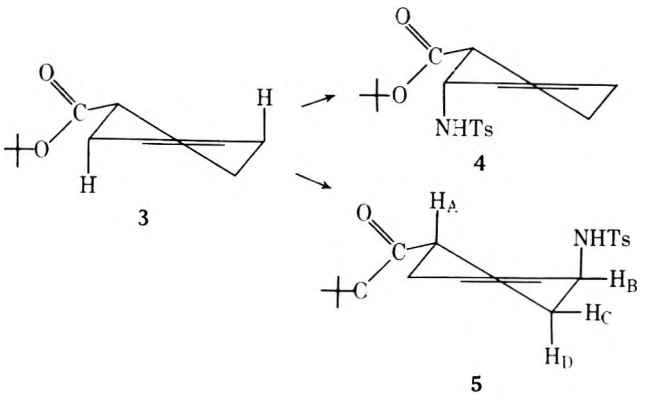
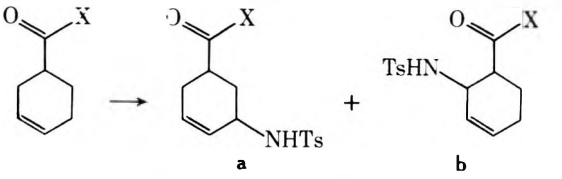


Although the relative stereochemistry of **4** and **5** are unimportant in terms of this particular synthesis, it is important from a mechanistic point of view and for general application to other complex cyclohexenyl systems. Allylic oxidation of conformationally fixed systems by the ene/(2,3) rearrangement pathway preferentially involves the replacement of a pseudoaxial hydrogen by a pseudoaxial substituent. For example, reaction of either SeO_2[12] or TsN=Se=NTs[3] with cholesterol results in the formation of the 4β (axial) alcohol or sulfonamide, respectively. This preference for pseudoaxial hydrogens is a consequence of the need for maximum orbital overlap in the transition state of the ene reaction.[13] Using this reasoning, the allylic sulfonamide **4** is predicted to be the cis and **5** the trans isomer.

The cis relationship in **4** was evident from the NMR decoupling experiments previously mentioned. The observed coupling constant (J = 3.4 Hz) is only consistent with the cis isomer; the corresponding trans compound should have J = 10 Hz at the minimum. When **4** was treated with strong base (potassium *tert*-butoxide in THF) in an attempt to epimerize it to the presumably more stable diequatorial (trans) isomer, only *p*-toluenesulfonamide was isolated, probably originating from an antiperiplanar elimination of the axial sulfonamide moiety. The trans relationship in **5** was demonstrated by both NMR and chemical correlations. High-field NMR (270 MHz)[14] showed a symmetrical eight-line AB portion of an ABXX′ pattern (centered at approximately δ 2.1 in benzene-d_6) for the H_C/H_D methylene group in **5**. Irradiation at δ 4.05 (the allylic proton α to sulfonamido group) caused a collapse of the multiplet to an "AB quartet" (J_{AB} = 11.77 Hz) and J_{BC} and J_{BD} was determined as 6.62 Hz and 8.09 Hz, respectively. These values indicated that H_B is pseudoequatorial and therefore, the sulfonamido group is pseudoaxial. The coupling constants involving H_A could not be determined because of obscuring signals. Similar coupling constants were found in the assignment of stereochemistry for the products of Pd-catalyzed allylic alkylation of *trans*-3-acetoxy-5-carbomethoxycyclohexene.[15] In an attempt to epimerize **5** to the diequatorial (cis) isomer, it was treated with excess potassium *tert*-butoxide in THF. However, the only product isolated (74% yield, mp 162–165 °C) was not the expected *tert*-butyl ester, but rather a carboxylic acid (**6**). This acid (**6**) was completely different from the carboxylic acid (**7**) formed from **5** by treatment with trifluoroacetic acid (76%, mp 174–175 °C). However, treatment of **7** with excess potassium *tert*-butoxide in THF gave **6** in 61% isolated yield. When **6** was heated in *t*-BuOH with a catalytic amount of H_2SO_4, (150 °C, combustion tube) a *tert*-butyl ester different from **5** was formed; however, the extremely poor yield did not allow for complete purification and characterization of this compound.

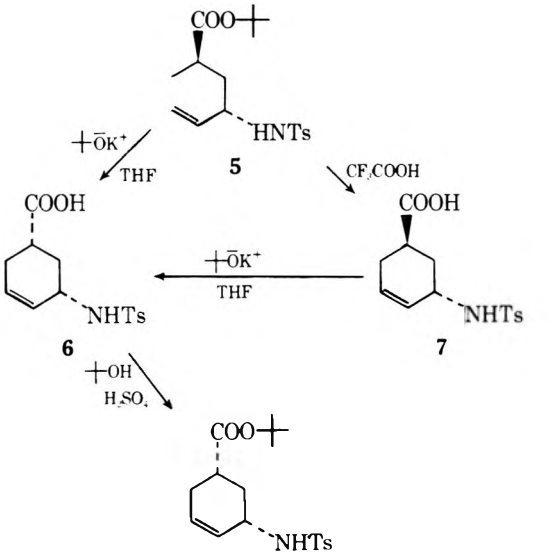
The hydrolysis of **5** to the carboxylic acid **6** under these conditions is not without precedent. Hydrolysis of hindered esters by potassium *tert*-butoxide has been known for many years, although the conditions needed are usually quite vigorous.[16] A possible mechanism is base-catalyzed elimination of *t*-BuOH to form a ketene which is then trapped by KOH (normally found as an impurity in commercial potassium *tert*-butoxide).[17]

Table I

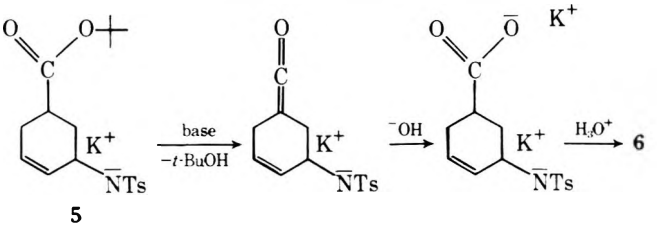


X	Registry no.	Reagent	Equivalents	Total yield	Ratio (b:a)[a]
-OCH_3	49543-03-5	S	1.2	80%	2:3[b]
		Se	1.25	49%	1:1[b]
-O-*tert*-Butyl	65121-09-7	S	1.25	70%	1:3
		Se	1.25	45%	1:1
$-OCHPh_2$	65121-10-0	S	5	50%	1:4
		Se	5	---[c]	----
-2,4,6-Trimethylphenol	65121-11-1	S	5	40%	1:6
		Se	5	---[c]	----
-*N*,*N*-Dicyclohexylamine	65121-12-2	S	5	32%	1:20

[a] Ratio determined by NMR integration. [b] Ratio confirmed by GLPC. [c] No allylic sulfonamide could be isolated.



In order to improve the positional selectivity of the allylic amination reaction, a survey of different ester derivatives was undertaken (Table I). The compounds listed in Table I were all (except for the methyl ester) prepared by reaction of the acid chloride with the appropriate alcohol or amine. The isomer ratio in the product mixture (isolated by chromatography) was determined by NMR integration of the allylic sulfonamide protons (generally found around δ 4.0). By analogy with compounds **5** and **6**, the signal at lower field was assigned



to the 2-*p*-toluenesulfonylamido isomer (b) and the upper field signal to the 5 isomer (a). Two trends can be observed in Table I; first, the sulfur-based reagent is more sensitive to steric factors than the selenium reagent, and secondly, the

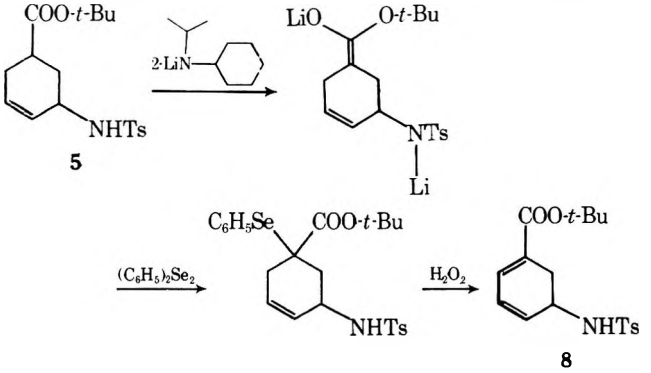
Table II. Methods for Cleavage of Sulfonamide Groups

Method	Ref
Electrochemical	23
(a) Tetramethylammonium amalgam/MeOH	24
(b) Pb cathode/NaOH in aqueous methanol	25
(c) DMF/$R_4N^+X^-$ (controlled potential)	23
(d) $CH_3CN/R_4N^+X^-$ (controlled potential)	26
Sodium napthalene	27, 28
Sodium bis(2-methoxyethoxy)aluminum hydride	29
Sodium–ammonia	30
HBr–phenol	31
Pyridine hydrochloride	31
50% Sodium amylate	31
Concentrated HCl	31

isolated yield of product is reduced when the steric bulk is increased. In the case of the *N,N*-dicyclohexylamine derivative, the allylic amination can be directed almost exclusively to the 5 position; however, the yield of product is low. Because of this and potential difficulties with the hydrolysis of these very hindered compounds, it was decided to continue the synthesis with the *tert*-butyl ester **5**.

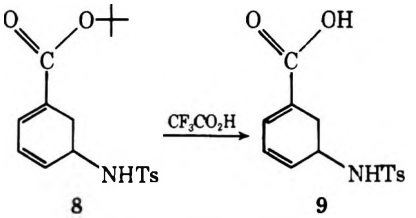
Having **5** in hand, the next step was the introduction of α,β-unsaturation in order to form the dienoic ester system. The classical and still widely used procedure for this type of transformation is halogenation–dehydrohalogenation. However, in recent years alternative methods, based on phenyl selenoxide eliminations[18,19] and on the related phenyl sulfoxide and methyl sulfoxide eliminations,[20] have been developed.

The dianion of **5** was generated with a slight excess of lithium cyclohexylisopropylamide in THF at −78 °C.[21] After quenching the enolate with 2 equiv of dry diphenyl diselenide, the resulting crude phenyl selenide (which was not isolated) was directly oxidized in THF at 0 °C with H_2O_2. From the reaction, the *tert*-butyl ester of *N*-*p*-toluenesulfonylgabaculine (**8**) was isolated in 82% yield as a white crystalline solid



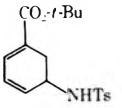
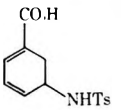
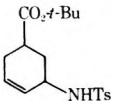
(mp 90–92 °C). Only traces of aromatic compounds were found.

Removal of the *tert*-butyl ester from **8** was accomplished by treatment with trifluoroacetic acid for 5 min at room temperature.[22] Removal of volatile material under high vacuum gave *N*-*p*-toluenesulfonylgabaculine (**9**) as a gummy



semisolid in quantitative yield. Unfortunately, all attempts at the recrystallization of **9** failed. In addition, **9** was somewhat thermally sensitive, decomposing to a dark, tarry material after about 1 day at room temperature. It was generally prepared as needed and used in crude form.

Table III. Comparison of Reduction Potentials

Compounds	Registry no.	$E_{1/2}$ (measd in 0.2 M TEAB[a] in MeOH)[b]
 8	65121-13-3	−1.73 V, −2.5 V
 9	65121-14-4	−2.12 V, −2.5 V
 5	65121-15-5	−2.34 V

[a] TEAB = tetraethylammonium bromide. [b] Vs. calomel reference electrode.

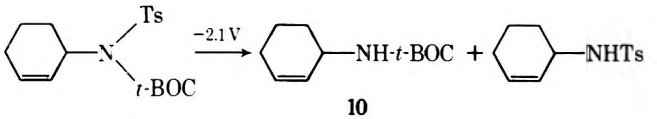
Only the cleavage of the *N*-*p*-toluenesulfonyl group of **9** remained in order to complete the synthesis of **1**. However, the lack of facile methods for the cleavage of sulfonamide groups has been a long-standing problem and many different approaches have been tried. Table II lists some of the methods. Because of the sensitive nature of the desired product, only the first two methods, electrochemical and sodium naphthalene, were considered worth trying.

When **9** was subjected to deprotection by either of these two methods under various conditions, no gabaculine was found. The only products which were isolated (in low yields) seemed by NMR to have one or both of the double bonds reduced. Similar treatment of **8** gave approximately the same results. The *tert*-butyl ester in **8** was stable to these reductive conditions.

In order to clarify the situation, the reduction potentials of **8** and **9**, as well as the saturated derivative **5**, were measured by polarography (Table III). The results indicate that the α,β-double bond is the most easily reducible function present ($E_{1/2}$ ranging from −1.73 to −2.12 V). The sulfonamide group is apparently not reduced until much higher potentials (approximately −2.4 V). This left two alternatives: (1) removal of the Ts group before the introduction of the α,β double bond and reprotection of the resulting amino group, or (2) lowering the reduction potential of the sulfonamide group below that of the double bond.

It is known[26,32] that electron-withdrawing substituents on aromatic sulfonamide groups lower the reduction potential. Alternatively, almost nothing is known about the effects of substitutions on the nitrogen of a primary sulfonamide. Using *N*-*p*-toluenesulfonylcyclohex-2-enamine[3] as a model substrate, the reduction potentials of a number of N-substituted derivatives were measured (Table IV). The compounds were prepared by alkylation (or acylation) of the sodium salt (prepared from the allylic sulfonamide plus NaH) in DMF with the appropriate reagent.

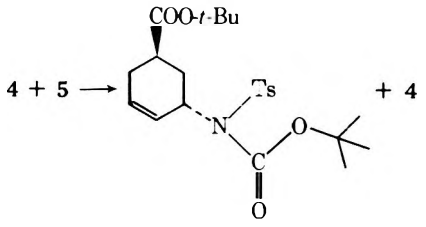
The use of an electron-withdrawing acyl group clearly reduces the reduction potential of the sulfonamide. The fact that the reduction wave is due to reduction of the Ts group was demonstrated by a preparative scale electrolysis of the *N*-tosyl-*tert*-butoxycarbonyl derivative at −2.1 V (0.2 M TEAB in MeCN). The only products isolated were the carbamate **10** (78% yield) and the starting allylic sulfonamide (22%). Unfortunately, the reduction potential of the sulfonamide was



10

still higher than the α,β double bond, so it became necessary to remove the protecting group before the unsaturation was introduced.

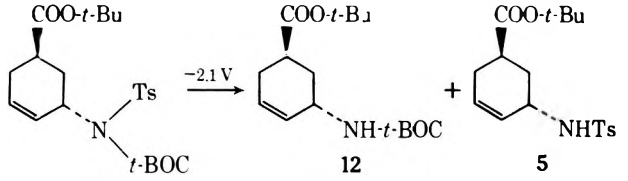
In an attempt to prepare the *t*-BOC derivative of **5**, a 20% 4/80% **5** mixture was subjected to 1.2 equiv of NaH in DMF, followed by 1.5 equiv of *tert*-butoxycarbonyl azide.[33] After heating at 70 °C for a few hours, the only product formed was **11** (100% based on **5**) while **4** was recovered (90% based on **4**).



11

These products were easily separated by column chromatography and so allowed for a convenient method of removing the "wrong" isomer without the need for a fractional recrystallization (and consequent loss of material).

The *N*-tosyl carbamate **11**, a yellow oil, had an $E_{1/2} = -2.06$ V. Preparative scale controlled potential electrolysis at −2.1 V (0.2 M TEAB/MeCN) gave, in analogy to the model compound, two products: the desired allylic carbamate **12** and the



11 12 5

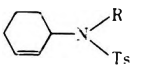
starting allylic sulfonamide **5**. The isolated yields depended on concentration and time of reaction, ranging from 76% **12** and 12% **5** (2.4 g of **11** in 100 mL of electrolyte, 3 h) to 64% **12** and 28% **5** (15.0 g **11** in 300 mL of electrolyte, 15 h). Although the origin of **5** was uncertain, one possible explanation was that the strong bases generated during the reduction cause the hydrolysis of the *tert*-butoxycarbonyl group. Addition of excess phenol (5 equiv) to act as a proton source[26] during the electrolysis prevented the formation of **5** and improved the yield of **12**. However, the isolated yields were still variable, ranging from 80% (4.8 g of **11** in 100 mL of electrolyte, 6 h) to 92% (0.6 g of **11** in 100 mL of electrolyte, 1.5 h).

The advantage of using a *tert*-butoxycarbonyl derivative in the previous reactions lies in its facile hydrolysis under mild acidic conditions, which allows it to be removed at the same time as the *tert*-butyl ester. Because of their acid sensitivity, *t*-BOC protecting groups have found much use in peptide chemistry.[34]

When **12** was subjected to the same reaction sequence (phenyl selenoxide elimination[18,19]) employed to dehydrogenate **5** to **8**, none of the corresponding diene **13** was found. The problem did not lie in the formation of the dianion (formed at −60 to −65 °C) nor in the quenching with diphenyl diselenide since the selenylated product was formed in good yield. Oxidation of the crude α-phenyl seleno ester by various methods (H_2O_2 in THF, H_2O_2 in CH_2Cl_2/pyridine, $NaIO_4$ in CH_3OH and Chloramine-T under phase transfer conditions) gave only complex mixtures of products.

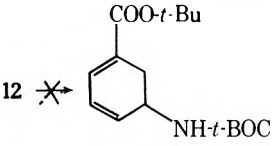
Since the phenyl selenoxide route did not seem viable for the formation of **13**, the dianion was alternatively quenched

Table IV. Effect of N-Substitution on Reduction Potentials

	Registry no.	$E_{1/2}$ (0.2 M TEAB[a] in MeCN)[b]
-H	65121-16-6	−2.31 V
$-CH_3$	65149-42-0	−2.30 V
$-CH_2Ph$	65120-92-5	−2.29 V
$-C(=O)CH_3$(Ac)	65120-93-6	−1.91 V
$-C(=O)OC(CH_3)_3$ (*t*-BOC)	65120-94-7	−2.06 V

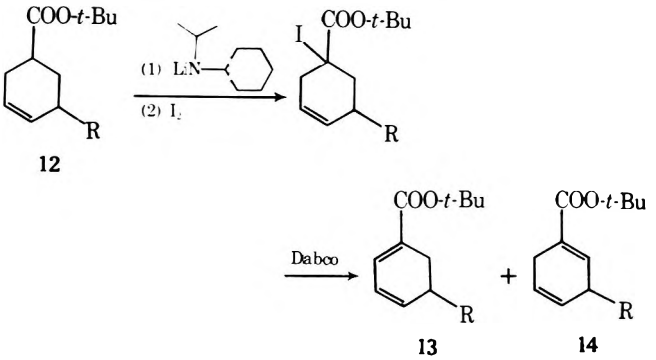
[a] TEAB = tetraethylammonium bromide. [b] Vs. calomel reference electrodes.

with iodine by the method of Rathke and Lindert.[35] The resulting crude α-iodo ester was then treated with base in benzene at room temperature to give **13** in 90% isolated yield. The



13

only other product isolated (9%) was the 2,5-dihydrobenzene derivative **14**, which was unstable in the presence of air and

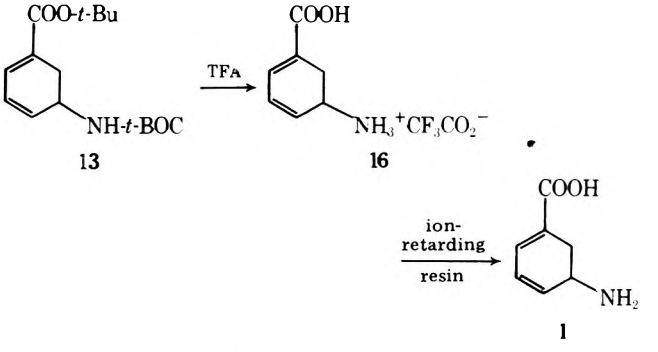


12 13 14

R = NH-*t*-BOC

quickly (10 min at room temperature) aromatized to the corresponding *m*-anthranilate ester **15**. Of the various bases tried (DBU, Dabco, and Et_3N), Dabco (diazobicyclo[2.2.2]octane) gave the highest yield and cleanest product mixture. GLPC analysis showed less than ½% of **5** present in **13**, which was a white crystalline solid, mp 99–101 °C.

The protecting groups of **13** were best removed by distilled trifluoroacetic acid under strictly oxygen-free conditions for 2 min followed by removal of the volatile material under high vacuum. The residue **16** (the trifluoroacetate salt of **1**) was

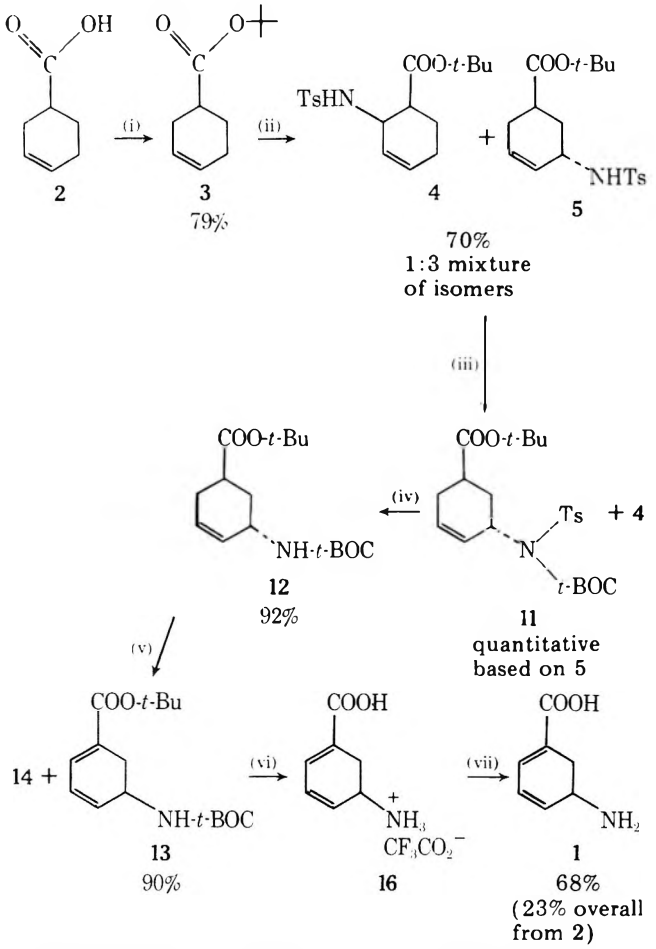


13 16 1

generally not isolated, but dissolved in H_2O and directly eluted through an ion-exchange resin. Use of undistilled CF_3CO_2H under the same conditions caused some aromatization to *m*-anthranilic acid.

Use of the cation-exchange resin SP Sephadex C-25 (used

Scheme I[a]



[a] (i) Isobutylene, H_2SO_4, ether, 25 °C; (ii) (a) 1.2 equiv of TsN=S=NTs, CH_2Cl_2, 25 °C; (b) K_2CO_3, in 60% CH_3OH–H_2O, (iii) (a) NAH, DMF, 25 °C; (b) *tert*-BOC azide; (iv) electrolysis (−2.1 V) in 0.2 M TEAB in MeCN; (v) (a) 3.6 equiv of lithium cyclohexylisopropylamide, THF, −78 °C; (b) I_2, THF, −78 °C; (c) DABCO, benzene, 25 °C; (vi) CF_3CO_2H; (vii) ion-retarding resin.

by Mishima to isolate 1 from the HCl salt[4]) or the related Dowex AG50W-X8 (Bio-Rad Laboratories) to isolate 1 was not totally satisfactory. When a solution of 2% NH_4OH was added in order to remove 1 from the resin, a dark brown, fluorescent impurity was formed which was difficult to separate from the gabaculine. The amount of this impurity was probably small since no peaks other than those of 1 were visible in the NMR spectra. The use of AG11A8 ion-retardation resin (Bio-Rad Laboratories)[36] gave much better results, since ammonium hydroxide was not necessary to remove 1 from the resin. Lyophilization of the appropriate fractions (identified by TLC with visualization by UV and ninhydrin test) gave *dl*-gabaculine (1) as an amorphous off-white powder in 68% yield from 13. This material, mp 194–196 °C dec (after recrystallization from aqueous MeOH, lit.[4] mp 196–197 °C dec) gave NMR, IR, and UV data consistent with the published values. The TLC behavior was identical with an authentic sample. A small sample of 1 was treated with HCl gas in MeOH at 0 °C to give *dl*-gabaculine hydrochloride salt, mp 195–199 °C dec (lit.[4] mp 198–200 °C dec) which gave an undepressed melting point upon admixture with an authentic sample of the racemic hydrochloride obtained from Mishima.

A summary of the exact route used to synthesize *dl*-gabaculine (1) is shown in Scheme I. This synthesis is comparable to Mishima's[4] both in terms of length and overall yield. Neither is without fault, particularly in the area of positional selectivity. However, one advantage of this synthesis is that the starting material, 3-cyclohexene-1-carboxylic acid, has been resolved via the brucine salt into the *R* and *S* enantiomers.[37] Although this has not been done, use of the optically active cyclohexene carboxylic acid 2 should lead to optically active gabaculine. Since only *l*-gabaculine is active toward γ-aminobutyrate aminotransferase,[4] this will have the effect of increasing the overall yield of the active agent.

Experimental Section

General Comments. Elemental microanalyses were performed by Midwest Microlab, Ltd. (Indianapolis, Ind.) and by Robertson Laboratory (Florham Park, N.J.). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected, as are the boiling points.

In general, reagent grade solvents were used without further purification. Tetrahydrofuran and benzene were always freshly distilled from purple sodium–benzophenone solutions under nitrogen. Chlorinated solvents (methylene chloride, chloroform, carbon tetrachloride) were used after passage through alumina and storage over 4 Å molecular sieves. All oxygen or water sensitive reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware (this will be called "anhydrous" conditions). Organic extracts of reaction mixtures were dried over anhydrous magnesium sulfate unless noted otherwise. Evaporation refers to removal of solvent under water aspirator pressure on a roto-vac (bath temperature <30 °C).

The following abbreviations will be used: t_r = GLC retention time under the specified conditions and R_f = TLC mobility relative to the solvent front (= 1).

Tetraethylammonium bromide (Eastman Organic Chemicals) was recrystallized from $CHCl_3/CCl_4$ and dried at 110 °C under vacuum for 12 h. Spectra-grade acetonitrile (stored over 4 Å sieves) was used for the electrochemical experiments (approximately the same results were found using acetonitrile which had been distilled first from CaH_2 and then from P_2O_5).

All ion-exchange resins were washed and prepared according to the manufacturer's instructions before use.

Polarographic measurements were made using a Princeton Applied Research Model 174A Polarographic Analyzer and a standard divided polarographic cell. Connection with the reference electrode (Corning Calomel catalog 476000) was by an Agar bridge (3–5% Difco Bacto-Agar in 1:1 saturated KCl/distilled H_2O). Solutions (generally 10^{-2} to 10^{-3} M) were deaerated by a N_2 stream for at least 3 min. Using 0.2 M TEAB in MeCN, the solvent discharge potential was −2.9 V.

Controlled potential electrolysis was performed using a Princeton Applied Research Model 371 potentiostat–galvanostat. Triply distilled Hg was used for the working electrode (cathode) and either a graphite rod or a Pt wire wrapped with Pt gauze for the counterelectrode (anode). The cell was divided by means of an unglazed, porous porcelain cup (Coors No. 70004) which had been previously extracted with refluxing acetone and then dried at 110 °C under vacuum. The electrolysis cell was flushed with a slow stream of N_2 and, before the addition of substrate, preelectrolyzed at a potential 100 mV more negative than the desired potential.

***tert*-Butyl 3-Cyclohexene-1-carboxylate (3).** Isobutylene was condensed at −78 °C (dry ice/isopropyl alcohol bath) in a 100-mL three-necked round-bottomed flask equipped with a dry ice condenser. Approximately 30–40 mL was transferred by cannula to a precooled Fisher-Porter pressure bottle containing 10.0 g (79.4 mmol) of 3-cyclohexene-1-carboxylic acid (Frinton Labs.) and 1 mL of concentrated H_2SO_4 in 20 mL of ether. The reaction vessel was sealed and allowed to warm to room temperature. After 14 h of stirring (magnetic), the pressure bottle was opened slightly (caution!) and the excess isobutylene was allowed to evaporate. After neutralizing the residue with $NaHCO_3$ (cooling was necessary), it was taken up in ether, which was washed twice with bicarbonate and once with brine, and dried. Filtration and evaporation afforded 13.94 g of a yellowish oil which was distilled (bp 44–46 °C at 0.6 Torr) to give 11.38 g (79%) of *tert*-butyl 3-cyclohexene-1-carboxylate as a clear oil: IR (film) 3030, 2980, 2930, 1730 (ester), 1475, 1455, 1435, 1390 (*tert*-butyl), 1370 (*tert*-butyl), 1310, 1230, 1160 (ester), 1000, 850 and 650 cm^{-1}; NMR ($CDCl_3$) δ 5.65 (2 H, broad s, olefinic), 2.4–1.8 (7 H, m, ring H) and 1.45 (9 H, s, *tert*-butyl). This reaction has been run on scales up to 35 g (0.28 mol) of acid with comparable results.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.40; H, 10.10.

Preparation of Bis(*N*-*p*-toluenesulfonyl)sulfodiimide

(TsN=S=NTs) from *N*-Sulfinyl-*p*-toluenesulfonamide (TsN=S=O). The *N*-sulfinyl-*p*-toluenesulfonamide used here was prepared by a modification of Kresze's[38] procedure; the details of our modified method are given in the accompanying paper[39] in this issue.

The following preparation of TsN=S=NTs follows Kresze's procedure.[38] *N*-Sulfinyl-*p*-toluenesulfonamide (98 g, 0.45 mol) was dissolved in 100 mL of dry benzene under a dry nitrogen atmosphere in a glovebag (due to the great moisture sensitivity of the product all of the following operations should be carried out under a dry atmosphere in a glovebag or a drybox). Dry pyridine (0.75 mL) was added, and the loosely stoppered (to allow for SO_2 evolution) flask was allowed to stand overnight in the glovebag with a slight flow of nitrogen passing through the bag. The sulfodiimide precipitated and was collected by filtration (in the glovebag). The yellow solid was washed twice with small portions of dry carbon tetrachloride and then dried under high vacuum to afford 75 g (90%) of bis(*N*-*p*-toluenesulfonyl)sulfodiimide, mp 40–45 °C (lit.[38] mp 48–50 °C). This compound is extremely sensitive to moisture and should be stored in a desiccator and handled only in the dry atmosphere of a glovebag or a drybox.

Reaction of TsN=S=NTs with 3. Preliminary Experiment. *tert*-Butyl 3-cyclohexene-1-carboxylate (0.91 g, 5 mmol) was added to a stirred solution of 3.45 g (9.3 mmol) of TsN=S=NTs in 15 mL of CH_2Cl_2 in a 50-mL round-bottomed flask under anhydrous conditions. After 3 days at room temperature, the dark reaction mixture was concentrated to a thick oil which was redissolved in 25 mL of 60% CH_3OH containing 3.0 g of K_2CO_3. After stirring overnight, the yellowish solution was taken up in 1:1 EtOAc/ether which was washed once with 1:1 4% NaOH/brine and brine, and dried. Filtration and evaporation left 2.02 g of yellowish oil which was purified by column chromatography (75 g of silica gel; eluted with EtOAc/hexane mixtures). After concentration of the appropriate fractions, 1.1 g (63%) of a pale yellow oil [R_f (35% EtOAc/hexanes) = 0.56] was recovered. NMR showed the product to consist of a mixture of two compounds (see text).

Repeated recrystallization from $CHCl_3$/hexanes produced a pure sample of one of the isomers which was identified as *cis*-*tert*-butyl 2-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylate (**4**), mp 120–121 °C: IR (KBr) 3170 (N–H), 2980, 1695 (H-bonded ester), 1595, 1455, 1390 (*tert*-butyl), 1370 (*tert*-butyl), 1340 (SO_2), 1310, 1160 (SO_2), 1075 and 920 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.9 (4 H, q, aromatic), 5.4 and 5.75 (2 H, m, olefinic), 4.95 (1 H, d, N–H), 4.1 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$), 1.8–2.4 (5 H, m, ring H) and 1.45 (9 H, s, *tert*-butyl). When the olefinic proton at δ 5.4 was irradiated ($CDCl_3$ containing 0.1 N NaOD/D_2O), the δ 4.1 multiplet collapsed to a doublet, J = 3.4 Hz. Irradiation at approximately δ 2.4 caused the same multiplet to collapse to a doublet, J = 7 Hz.

Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.98. Found: C, 61.41; H, 7.16; N, 3.70.

Concentration of the mother liquors from above and further recrystallization ($CHCl_3$/hexanes) gave the second isomer which was identified as *trans*-*tert*-butyl 5-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylate (**5**), mp 83–84 °C: IR (KBr) 3280 (NH), 2980, 1710 (ester), 1595, 1450, 1390 (*tert*-butyl), 1370 (*tert*-butyl), 1340 (SO_2), 1310, 1160 (SO_2), 1080 and 820 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.9 (4 H, q, aromatic), 5.35 and 5.75 (2 H, m, olefinic), 5.0 (1 H, d, NH), 3.9 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$), 1.8–2.4 (4 H, m, ring H) and 1.45 (9 H, s, *tert*-butyl).

Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.98. Found: C, 61.63; H, 7.24; N, 3.88.

Reaction of TsN=Se=NTs with 3. Preliminary Experiment. The selenium diimide reagent (7.5 mmol) was prepared by stirring a mixture of 0.69 g of selenium metal (8.7 mmol) and 3.42 g of anhydrous chloramine-T (15 mmol) in 20 mL of CH_2Cl_2 at room temperature for 20 h. *tert*-Butyl 3-cyclohexene-1-carboxylate (0.91 g, 5 mmol) was added to the resulting white slurry. After 2 days, the dark reaction mixture was quenched with 1:1 4% NaOH/brine. EtOAc/ether (1:1) was added and both phases were filtered through Celite. The organic phase was separated, washed once with 1:1 4% NaOH/brine and brine, and dried. Filtration and evaporation afforded about 3 g of crude product which was purified by column chromatography (as previously described) to give 790 mg (after 2 h in vacuo, 45%) of a slightly yellow oil. NMR integration of the multiplets at δ 4.1 and δ 3.9 showed an approximate (±10%) 1:1 mixture of **4** and **5**.

Allylic Amination of *tert*-Butyl 3-Cyclohexene-1-carboxylate (3). Best Conditions. *tert*-Butyl 3-cyclohexene-1-carboxylate (**3**) (27.5 g, 0.151 mol) was added to a stirred solution of 80.0 g of TsN=S=NTs (0.216 mol) in 300 mL of CH_2Cl_2 in a 500-mL round-bottomed flask under anhydrous conditions. After 8 days at room temperature, the reaction mixture was concentrated and the residue was redissolved in 300 mL of CH_3OH. Water (200 mL) was added followed by 70 g of K_2CO_3 in three portions. After 16 h, the reddish solution was taken up in 350 mL of 1:1 EtOAc/ether which was washed twice with 1:1 4% NaOH/brine and once with brine, and dried. Filtration and evaporation gave a dark red-yellow oil which was passed through a plug of silica gel (80 g) with 15% EtOAc/hexanes. Concentration of the filtrate gave 49.6 g of crude product. Trituration with 200 mL of cyclohexane while cooling (crystallization was usually induced by scratching or with seed crystals) afforded 33.33 g (after drying in vacuo) of a mixture of **4** and **5** (63%; by NMR, 20% **4** and 80% **5**), mp 89–95 °C.

The mother liquors from above were concentrated and chromatographed on 200 g of silica gel (packed with hexanes; eluted with 500 mL of hexanes, 5% EtOAc/hexanes, then 2 L of 10% EtOAc/hexanes; 100 mL fractions). Combination of appropriate fractions and evaporation afforded 5.9 g of a red-yellow oil. Recrystallization from cold cyclohexane as above gave an additional 4.03 g of the same mixture of **4** and **5** (total overall yield of the mixture of isomers 70%).

Reaction of 5 with Potassium *tert*-Butoxide. Potassium *tert*-butoxide (360 mg, 3.2 mmol, Aldrich Chemical Co.) was added to a stirred solution of 200 mg (0.57 mmol) of **5** in 10 mL of THF in a two-necked, round-bottomed flask under anhydrous conditions. After 36 h at room temperature, water was added and the reaction mixture acidified with 1 N HCl (to pH ~1) and extracted with 1:1 EtOAc/ether. The organic phase was washed once with brine and dried. Filtration and evaporation gave a yellowish oil which was recrystallized from $CHCl_3$/hexanes to give *cis*-5-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylic acid **6** (124 mg, 74%), R_f (10% EtOH/EtOAc) = 0.1, mp 162–165 °C: IR (KBr) 3600–3000 (broad band, carboxylic acid OH), 3250 (NH), 1735 and 1705 (carboxylic acid), 1595, 1450, 1400, 1325 (SO_2), 1295, 1250, 1235, 1150 (SO_2), 1075, 930, and 815 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 11.5 (1 H, broad s, exchangeable with D_2O, CO_2H), 7.2–7.9 (4 H, q, aromatic), 6.9 (1 H, d, NH), 5.2–5.8 (2 H, broad m, olefinic), 3.95 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$) and 1.8–2.5 (5 H, m, ring H). Equivalent results were obtained if the reaction mixture was refluxed for 1 h instead of stirring 36 h at room temperature.

Reaction of 5 with Trifluoroacetic Acid. One gram of **5** (2.85 mmol) was dissolved in 4.0 mL of trifluoroacetic acid. After 15 min, the volatile material was removed by high vacuum and the residue recrystallized ($CHCl_3$/hexanes). *trans*-5-(*p*-Toluenesulfonamido)-3-cyclohexene-1-carboxylic acid (0.64 g, 76%) **7**, R_f (10% EtOH/EtOAc) = 0.65, was obtained: mp 174–175 °C; IR (KBr) 3600–3000 (broad band, carboxylic acid), 3360 (NH), 1740 and 1705 (carboxylic acid), 1595, 1455, 1405, 1325 (SO_2), 1295, 1250, 1235, 1150 (SO_2), 1075, 930, 885, and 815 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 11.0 (1 H, broad s, CO_2H), 7.2–7.9 (4 H, q, aromatic) 7.05 (1 H, d, NH), 5.6 and 5.35 (2 H, m, olefinic), 3.95 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$) and 1.8–2.5 (5 H, m, ring H). While the spectra of **6** and **7** were similar, they were not superimposable.

Isomerization of 7 to 5 with Potassium *tert*-Butoxide. A stirred mixture of 75 mg of **7** (0.25 mmol) and 200 mg (1.8 mmol) of potassium *tert*-butoxide in 5 mL of THF was refluxed for 3 h in a 25-mL round-bottomed flask fitted with a reflux condenser under anhydrous conditions. After cooling, the mixture was quenched with H_2O, acidified with 1 N HCl, and then extracted with EtOAc. The organic phase was washed once with brine and dried. Filtration and evaporation gave a yellowish oil (82 mg) which was recrystallized twice from $CHCl_3$/hexanes to give a white solid (46 mg, 61%) which was identical (TLC, NMR, and IR) with **6**.

***tert*-Butyl 3-(*p*-Toluenesulfonamido)-2,3-dihydrobenzoate (8).** *trans*-*tert*-Butyl 5-(*p*-toluenesulfonamido)-3-cyclohexene-1-carboxylate **5** (1.05 g, 2.99 mmol) was added to a stirred and cooled (−78 °C, dry ice/isopropyl alcohol) solution of lithium cyclohexylisopropylamide (prepared at −78 °C by the addition of 3.0 mL of 2.4 M (7.2 mmol) *n*-BuLi in hexanes to 1.38 mL (7.6 mmol) of cyclohexylisopropylamine in a 100-mL three-necked, round-bottomed flask under anhydrous conditions). After ½ h, a precooled (−78 °C) solution of 2.34 g (7.5 mmol) diphenyl diselenide (recrystallized from hexanes and dried in vacuo) in 10 mL of THF was added quickly by cannula using positive N_2 pressure. After 2.5 h with gradual warming to room temperature, the reaction was quenched with water (25 mL) and extracted twice with 1:1 EtOAc/ether. The organic phase was washed once with H_2O, 1 N HCl, bicarbonate and brine, and then dried. Filtration and evaporation afforded a yellow oil, which was redissolved in 50 mL of THF, cooled to 0 °C (ice bath), and 3.4 g of 30% H_2O_2 (30 mmol) added in three portions over 1.5 h. After another 1.5 h at room temperature, the colorless reaction mixture was taken up in 1:1 ether/EtOAc which was washed once with bicarbonate and brine, and dried. Filtration and evaporation gave 1.45 g of a light yellowish oil.

This material, although fairly pure by TLC, was best purified by column chromatography (60 g of alumina activity III, eluted with EtOAc/hexane mixtures). Concentration of the appropriate fractions gave 960 mg of a slightly yellow oil, which upon trituration with cyclohexane gave *tert*-butyl 3-(*p*-toluenesulfonamido)-2,3-dihydrobenzoate 8 (840 mg, 82%) as a white crystalline solid. R_f (35% EtOAc/hexanes) = 0.63, mp 90–92 °C; IR (KBr) 3250 (NH), 2980, 1725, and 1705 (ester), 1595, 1580, 1440, 1370, 1330 (SO_2), 1160 (SO_2), 1095, and 810 cm^{-1}; NMR ($CDCl_3$) δ 7.25–7.9 (4 H, q, aromatic), 6.95 (1 H, d, α-hydrogen), 5.8–6.2 (2 H, m, olefinic), 5.0 (1 H, d, exchangeable with 0.1 N NaOD/D_2O, NH), 4.1 (1 H, m, collapses to d of d in base, allylic R_2CHN), 2.6 (2 H, d of d, $-CH_2-$), 2.45 (3 H, s, aromatic $-CH_3$) and 1.5 (9 H, s, *tert*-butyl); UV_{max}(MeOH) 239 nm (log ε 4.07) and 283 nm (ε 4225).

Anal. Calcd for $C_{18}H_{23}NO_4S$: C, 61.86; H, 6.63; N, 4.00. Found: C, 61.92; H, 6.80; N, 3.78.

***N*-(*p*-Toluenesulfonyl)gabaculine (9).** The diene 8 (50 mg, 0.14 mmol) was dissolved in 1 mL of CF_3CO_2H under N_2. After 5 min, the solvent was removed under high vacuum to afford a gummy residue. This material (42 mg, 100%) was temperature sensitive and could not be recrystallized (CCl_4, $CHCl_3$/hexanes, aqueous EtOH): NMR ($CDCl_3$) δ 8.05 (1 H, d, α-hydrogen), 7.2–7.8 (6 H, m, aromatic and olefinic), 5.15 (1 H, m, allylic R_2CHN), 5.00 (1 H, d, NH), 2.8 (2 H, m, $-CH_2-$) and 2.45 (3 H, s, aromatic $-CH_3$). Cleavage of the *tert*-butyl ester with HCl gas in CH_2Cl_2 at −10 °C (1 h), followed by concentration by high vacuum, gave the same material. Because of its gummy nature and instability, **9** was generally not isolated.

***trans-tert*-Butyl 5-(*N*-*tert*-Butoxycarbonyl-*p*-toluenesulfonamido) 3-cyclohexene-1-carboxylate (11).** The allylic sulfonamide mixture obtained by allylic amination of **3** (20% **4**/80% **5**, 25 g, 71.2 mmol) was added in small portions with stirring and cooling (ice bath) to a suspension of 4.3 g of NaH (50% in oil, 89.6 mmol) in 250 mL of DMF in a 500-mL round-bottomed flask under anhydrous conditions. After warming to room temperature (1 h), *tert*-butoxycarbonyl azide[33] (15.3 g, 106.9 mmol) was added. After heating at 60–70 °C for 13 h, the reaction was cautiously quenched with small pieces of ice. EtOAc/ether (1:1, 250 mL) was added and the organic phase washed three times with H_2O and once with brine, and dried. Filtration and evaporation afforded 43.4 g of yellowish oil.

Column Chromatography (400 g of Silica Gel, Eluted with EtOAc/Hexanes). Concentration of the appropriate fractions afforded 25.69 g (dried 5 h in vacuo, 80%, 100% based on **5**) of **11** as a thick yellowish oil, R_f (25% EtOAc/hexanes) = 0.64: IR (film) 2980, 2940, 1740–1705 (broad band; ester and carbamate), 1595, 1480, 1460, 1395, and 1370 (*tert*-butyl), 1360 (SO_2), 1260, 1160 (SO_2), 1090, 850, 835, 820, and 740 cm^{-1}; NMR ($CDCl_3$) δ 7.25–7.95 (4 H, q, aromatic), 5.5–6.0 (2 H, m, olefinic), 5.2 (1 H, m, allylic R_2CHN), 2.45 (3 H, s, aromatic $-CH_3$), 2.0–2.5 (4 H, m, overlapping $-CH_2-$), 1.55 (9 H, distorted t, *tert*-butyl) and 1.45 (9 H, s, *tert*-butyl); mass spectrum (70 eV) *m/e* 451 (M^+), 395 (M − 56, loss of isobutylene), 339 (M − 112, loss of two isobutylene + CO_2), 216, 183, 139, 84, and 82 (base peak). The NMR signal at δ 1.55 is assigned to the *tert*-butoxycarbonyl group; the splitting is possibly caused by hindered rotation because of the *N*-tosyl group. The trans stereochemistry is assumed on the basis of the starting material.

Anal. Calcd for $C_{23}H_{33}NO_6S$: C, 61.17; H, 7.36; N, 3.10. Found: C, 60.90; H, 7.36; N, 3.11.

Further elution of the column and concentration of the appropriate fractions gave 5.57 g of crude **4** [R_f (25% EtOAc/hexanes) = 0.45]. Recrystallization from $CHCl_3$/hexanes afforded a total (2 crops) of 4.37 g (17.5%, 90% recovery based on **4**) of **4** which was identical with the previously isolated material.

Controlled Potential Electrolysis of 11. In an electrolysis cell, 2.43 g (5.4 mmol) of **11** was added to 100 mL of preelectrolyzed 0.2 M TEAB/MeCN at −2.1 V (residual current = 1 mA). The current initially rose to 450 mA and then decayed to 10 mA after 3 h. TLC (25% EtOAc/hexanes) showed no starting material remaining, so water (100 mL) was added and the dark solution was extracted with ether. The organic phase was washed once with water and brine, and dried. Filtration and evaporation left a yellowish oil. Column chromatography (80 g of silica gel, eluted with EtOAc/hexanes) afforded 320 mg (17%) of **5**, R_f (25% EtOAc/hexanes) = 0.45 (identical with a previously isolated sample), and 1.22 g (after 2 h in vacuo, 76%) of **12** as a clear oil, which solidified upon standing, R_f (25% EtOAc/hexanes) = 0.71. Recrystallization from a minimum amount of petroleum ether (1 mL/1 g) gave fluffy white crystals, mp 65–68 °C: IR (KBr) 3390 and 3320 (NH), 2980, 2930, 1735 (ester), 1710 (carbamate), 1520, 1395 and 1370 (*tert*-butyl), 1320, 1250, 1160, 1055, 1045, 870 and 850 cm^{-1}; NMR ($CDCl_3$) δ 5.7 (2 H, m, olefinic), 4.55 (1 H, m, NH), 4.25 (1 H, m, allylic R_2CHN), 1.45 (9 H, s, *tert*-butyl) and 1.2–2.4 (5 H, m, ring H); mass spectrum (70 eV) *m/e* 297 (M^+), 262 (M − 15, loss of CH_3), 241 (M − 56, loss of isobutylene), 224 (M − 73, loss of *tert*-butoxy) and 185 (base peak, M − 112, loss of two isobutylenes).

Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.61; H, 9.15; N, 4.71. Found: C, 64.43; H, 9.14; N, 4.48.

When the reaction was repeated using 15.0 g (33.2 mmol) of **11** in 300 mL of 0.2 M TEAB/MeCN, 15 h was needed for completion. Isolation in the same manner (300 g of silica gel) afforded 6.29 g (64%) of **12** and 3.23 g (28%) of **5**.

Controlled Potential Electrolysis of 11 in the Presence of Phenol. The *N*-tosylcarbamate **11** (4.82 g, 10.7 mmol) was added to a preelectrolyzed solution of 5.0 g of phenol (53 mmol) in 100 mL of 0.2 M TEAB/MeCN at −2.1 V (residual current = 8 mA). After 6 h (the electrolysis was slightly exothermic), the current had decayed to 17 mA. Isolation as previously described gave 2.66 g (84%) of crude product. Trituration with 2 mL of petroleum ether afforded 2.45 g (total of 2 crops, 80%) of **12**.

Using 590 mg (1.3 mmol) of **11** and 650 mg (6.8 mmol) of phenol (under exactly the same conditions), 380 mg (98%) of crude product was obtained. Recrystallization from petroleum ether gave a total (2 crops) of 357 mg (92%) of **12**.

***tert*-Butyl 3-(*tert*-Butoxycarbonylamino)-2,3-dihydrobenzoate (13). Dehydroiodination.** A solution of cooled (−78 °C) lithium isopropylcyclohexylamide was prepared using 10.75 mL (24.6 mmol) of 2.4 M *n*-BuLi and 4.5 mL (24.7 mmol) of isopropylcyclohexylamine in 40 mL of THF in a 100-mL three-necked round-bottomed flask. The allylic carbamate **12** (2.0 g, 6.7 mmol) was added and after 10 min the cooling bath was changed to one maintained at −65 to −60 °C for 1 h. The resulting clear yellow solution of dianion was added using a cannula and positive N_2 pressure to a cooled (−78 °C) and stirred solution of 6.26 g (24.7 mmol) of I_2 in 30 mL of THF in a 250-mL round-bottomed flask under anhydrous conditions. After 2 h, the cooling bath was replaced by an ice bath for another 1.5 h. After an additional ½ h at room temperature, the reaction was quenched with water (20 mL) and extracted with ether which was washed once with cold 1 N HCl, with aqueous sodium bisulfite until colorless, then once with bicarbonate, and brine, and finally dried.

Filtration and evaporation gave a light yellowish oil which was immediately dissolved in 80 mL of benzene and 2.0 g (17.8 mmol) of diazabicyclo[2.2.2]octane (Dabco) was added in one portion. After stirring overnight, the reaction was taken up in ether which was washed once with cold 1 N HCl, bicarbonate, and brine, and dried. Concentration afforded 2.6 g of yellowish oil which was purified by column chromatography (200 g of silica gel, eluted with EtOAc/hexanes) to give two compounds, A and B.

Compound A (180 mg of a white semisolid, 9%) was tentatively identified as *tert*-butyl 5-(*tert*-butoxycarbonylamino)-2,5-dihydrobenzoate (**14**), R_f (25% EtOAc/hexanes) = 0.64: NMR ($CDCl_3$) δ 6.8 (1 H, m, α-hydrogen of α,β-unsaturated ester), 5.6–6.0 (2 H, m, olefinic), 4.9 (1 H, m, NH), 4.7 (1 H, m, allylic R_2CHN), 2.9 (2 H, d, allylic $-CH_2-$), 1.5 (9 H, s, *tert*-butyl) and 1.45 (9 H, s, *tert*-butyl).

This compound was unstable in the presence of air, decomposing completely to *tert*-butyl *N*-(*tert*-butoxycarbonyl)-*m*-anthranilate (**15**), R_f (25% EtOAc/hexanes) = 0.76, mp 112–115 °C (recrystallized from $CHCl_3$/hexanes): IR (KBr pellet) 3340 (NH), 2980, 2930, 1715–1680 (broad band, ester and carbamate), 1510, 1390, and 1370 (*tert*-butyl), 1305, 1245, 1170, 1110, 870, and 855 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.9 (4 H, m, aromatic), 7.0 (1 H, broad s, NH), 1.55 (9 H, s, *tert*-butyl) and 1.5 (9 H, s, *tert*-butyl).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 65.39; H, 8.11; N, 4.79.

Compound B (1.80 g of a clear oil) was triturated with approximately 1 mL of petroleum ether to afford 1.78 g (90%) of *tert*-butyl 3-(*tert*-butoxycarbonylamino)-2,3-dihydrobenzoate (**13**) as a fluffy white solid, R_f (25% EtOAc/hexanes) = 0.57: mp 99–101 °C; IR (KBr) 3350 (NH), 2980, 2930, 1720–1680 (broad band, ester, and carbamate), 1510, 1395, and 1370 (*tert*-butyl), 1280, 1255, 1165, 1095, 1050, 850, 760, and 720 cm^{-1}; NMR ($CHCl_3$/hexanes) δ 7.0 (1 H, m, α-hydrogen, 6.1 (2 H, m, olefinic), 4.9 (1 H, m, allylic R_2CHN), 2.6 (2 H, d of d, methylene), 1.5 (9 H, s, *tert*-butyl), and 1.45 (9 H, s, *tert*-butyl); mass spectrum (70 eV) *m/e* 295 (M^+), 260, 239 (M − 56, loss of isobutylene), 183 and 139 (base peak); UV_{max}(MeOH) 284 nm (ε 6240); GLPC analysis (2 m × 2 mm, 5% OV-17 on 80/100 mesh Gas Chrom Q, 195 °C) of **13** (t_r = 3.4 min) showed it to be contaminated with less than ½% of **12** (t_r = 2.9 min).

Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.05; H, 8.53; N, 4.74. Found: C, 64.94; H, 8.32; N, 4.55.

***dl*-Gabaculine (1).** The diene **13** (511.2 mg, 1.7 mmol) was dissolved in 1.5 mL of purified trifluoroacetic acid (distilled at 72 °C under N_2 and stored in a no-air container) under oxygen-free condi-

tions (exothermic reaction). After 2 min, all of the volatile material was removed under high vacuum leaving, after 2 h, a dark semisolid residue. Addition of a little distilled H_2O caused a white crystalline solid to precipitate (presumably the trifluoroacetate salt of 1). After warming gently to redissolve the solid, the solution was applied to a 1 × 20 cm column of Bio-Rad AG11A8 ion-retardation resin[36] and eluted with distilled H_2O. Lyophilization of the appropriate fractions (generally the first 3–10 mL of eluent, visualized by UV and ninhydrin test after spotting on a TLC plate) gave 169 mg (70%) of crude *dl*-gabaculine (1), mp 180–185 °C dec (lit.[4] mp 196–197 °C dec). Recrystallization from MeOH containing a minimum amount of H_2O gave 2 crops of an off-white solid: first crop (83 mg), mp 184–186 °C dec; second crop (32 mg), mp 194–196 °C dec. A third crop (49 mg, mp 182–186 °C dec) was recovered by addition of ether to the mother liquors for a total of 164 mg (68%) of 1: $UV_{max}(H_2O)$ 275 nm (ϵ 8500) (lit.[4] 275 nm (ϵ 8600)). NMR and IR data were consistent with the published values.[4] TLC analysis (7.5 EtOH, 2.5 H_2O, trace NH_4OH) showed a single spot, R_f = 0.64, which cospotted with an authentic sample derived from *dl*-gabaculine hydrochloride.

***dl*-Gabaculine Hydrochloride Salt.** *dl*-Gabaculine (mp 194–196 °C from above, 5 mg, 36 μmol) was dissolved in 0.5 mL of cooled (ice bath) absolute MeOH which had been saturated with dry HCl gas. The solvent was immediately removed by high vacuum to afford a white solid. Recrystallization from acetone containing a little methanol gave 4 mg (63%) of *dl*-gabaculine hydrochloride, mp 195–199 °C dec (lit.[4] mp 198–200 °C dec). Admixture with an authentic sample of racemic gabaculine hydrochloride had no effect on the melting point.

Acknowledgment. We kindly thank Dr. Mishima for copies of the original NMR spectra of 1 and its HCl salt, the experimental details of his synthesis, and for the authentic sample of *dl*-gabaculine hydrochloride. We are indebted to the National Institutes of Health (GM 21686) and the National Science Foundation (MPS 74-21260) for financial support. We are grateful to our colleagues, Harold R. Rogers and George M. Whitesides, for assistance using their preparative electrolysis equipment.

Registry No.–1, 59556-18-2; 1·HCl, 59556-17-1; 4, 65120-95-8; 6, 65120-96-9; 7, 65120-97-0; 11, 65120-98-1; 12, 65120-99-2; 13, 65121-00-8; 14, 65121-01-9; 15, 65121-02-0; TsN=S=NTs, 851-06-9; TsN=Se=NTs, 60123-29-7; isobutylene, 115-11-7; 3-cyclohexene-1-carboxylic acid, 4771-80-6; *N*-sulfinyl-*p*-toluenesulfonamide, 4104-47-6; selenium, 7782-49-2; chloramine-T, 127-65-1; trifluoroacetic acid, 76-05-1; lithium cyclohexylisopropylamine, 32400-20-7; diphenyl diselenide, 1666-13-3; *tert*-butoxycarbonyl azide, 1070-19-5.

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Notes

Allylic Deuteration and Tritiation of Olefins with *N*-Sulfinylsulfonamides

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Recently, we have explored the synthetic applications of the reactions of both bis(*N*-*p*-toluenesulfonyl)selenodiimide[1-3] and bis(*N*-*p*-toluenesulfonyl)sulfodiimide.[4,5] These aza analogues of SeO_2 and SO_2 are powerful enophiles in their reactions with olefins and eventually result in the formation of allylic sulfonamides. Kresze and Schönberger independently discovered that the sulfur diimide species effect allylic amination of olefins.[6] We now report that the ene reaction[7] of the related monooxo compounds, the *N*-sulfinylsulfonamides,[8] is reversible under mild conditions and that this reversibility can be exploited to specifically introduce deuterium (or tritium) into the allylic position of an alkene.

When 1.1 equiv of **1** was stirred with β-pinene in benzene for 3 h at 25 °C, a 1:1 adduct, the *N*-tosylsulfinamide **3**, was isolated in 89% yield (Scheme I). However, upon standing in moist air at room temperature for a few days or upon strong heating (>150 °C), **3** was found to decompose with the liberation of β-pinene. When **3** was refluxed in benzene, no change occurred until an excess of H_2O was added which resulted in the formation of β-pinene and *p*-toluenesulfonamide. The observed behavior is consistent with a reversible ene reaction. However, initial hydrolysis of the allylic sulfinamide adduct to an allylic sulfinic acid, which then undergoes retroene reaction, is another possibility.

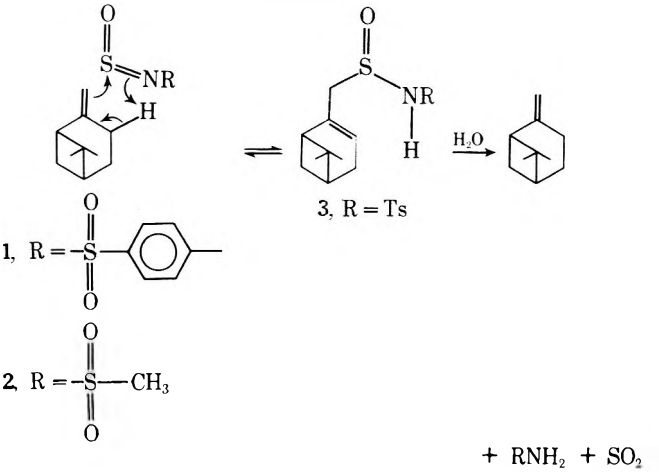
When the H_2O was replaced by D_2O, exchange of the acidic N–H proton followed by retroene reaction led to the incorporation of a deuterium in the allylic position. In the case of β-pinene (Scheme II), the recovered material was 86% d_1 and 14% d_0 with the deuterium being introduced trans (>97%) to the dimethyl bridge as shown by ^2H NMR[9,10] and confirmed by the loss of the deuterium upon oxidation with SeO_2 to *trans*-pinocarveol.[11] These results are similar to the stereospecific retroene reaction of the deuterated adduct of β-pinene and methyl phenyl glyoxylate[10] with the exception that in the present case much lower temperatures are needed.

Table I shows the results for the allylic deuteration of a variety of olefins. Generally, the olefins were recovered in yields greater than 50% and greater than 75% monodeuterated. It was not necessary to isolate the initial ene adduct. It should be pointed out that the reaction is not general since some cyclic olefins as well as electron-poor or hindered olefins are poor substrates for this system. Among the compounds which failed to form an isolable ene adduct were cyclohexene, 4-*tert*-butylcyclohexene, Δ^2-cholestene, cholesterol, and α-pinene. Under forcing conditions, 4-*tert*-butylcyclohexene gave *tert*-butylbenzene in good yield.[12]

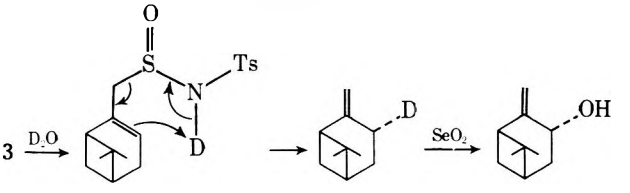
l-Carvone is the only example in Table I of an olefin with exchangeable protons. Exchange of the crude deuterated product with ethanolic NaOH at 60 °C for 3 h gave *l*-carvone that was >75% d_1. NMR integration indicated that the deuterium was located in the vinyl methyl group (although Büchi and Wüest[13] have shown that the major product of SeO_2 oxidation of *l*-carvone is the racemic tertiary allylic alcohol). In support of the proposed location of the deuterium, the initial 1:1 adduct was found to have the structure **5**.[15] In addition, there was no loss in the optical activity of the recovered deuterated *l*-carvone. During the reaction, some aromatization[12] of the *l*-carvone to dehydrocarvacrol (2-methyl-5-isopropenylphenol) occurred.

Of course, alkenes can be tritiated in the same manner using T_2O in place of D_2O. As shown in Scheme III, α-methylstyrene with a specific radioactivity of 0.8 mCi/mmol was isolated when 2 mmol of its crystalline adduct **5** was refluxed for 20 h in 5 mL of benzene containing 0.1 mL of T_2O (1 Ci/mL). Correcting for the 2 mmol of protons introduced with the adduct **5**, the specific activity of the medium was 7.7 mCi/mmol of H^+. Therefore tritium was incorporated into the olefin at a specific radioactivity 10% that of the reaction medium. This calculation is based on the notion that only one allylic hydrogen is available for exchange. This would be true if the *N*-sulfinylsulfonamide (TsN=S=O) hydrolyzed as it

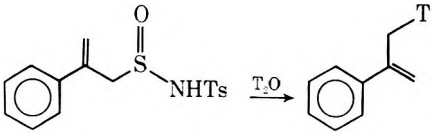
Scheme I



Scheme II



Scheme III



5

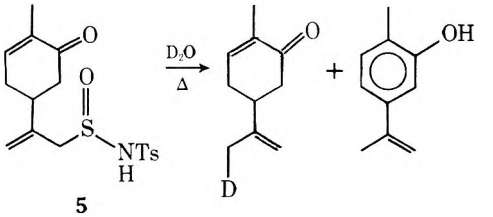


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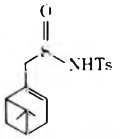
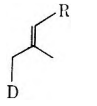
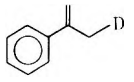
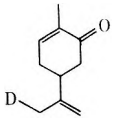
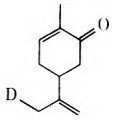
Table I. Allylic Deuteration of Alkenes

Case	Olefin	Registry no.	Reagent[b]	Product[a]	Registry no.	Deuterium incorporation[a]	Recovery[c]
1	β-Pinene	127-91-3	1.2 TsNSO[e]		65025-52-7	14% d_0 86% d_1	59%
2	β-Pinene		2 MsNSO[f]			3% d_0 94% d_1 4% d_2	51%
3		64976-20-1				4% d_0 95% d_1 3% d_2	78%
4	1-Dodecene	112-41-4	3 TsNSO		64976-21-2	4% d_0 93% d_1 2% d_2	46%
5	Citronellol methyl ether	55915-70-3	2 TsNSO		64976-22-3	11% d_0 87% d_1 2% d_2	68%
6	α-Methyl-styrene	98-83-9	1.2 TsNSO		64976-23-4	15% d_0 84% d_1 1% d_2	79%
7	l-Carvone	6485-40-1	2 TsNSO		64976-24-5	(Crude)(Exchanged) 13% d_0 16% d_0 46% d_1 82% d_1 35% d_2 2% d_2 6% d_3	39% (After exchange)
8	l-Carvone		2 MsNSO			(Crude)(Exchanged) 16% d_0 16% d_0 20% d_1 37% d_2 75% d_1 25% d_3 2% d_4 9% d_2	39% (After exchange)

[a] See the Experimental Section for all details. The location of the deuterium was determined by NMR. [b] TsNSO = *N*-sulfinyl-*p*-toluenesulfonamide. MsNSO = *N*-sulfinylmethanesulfonamide. The numbers refer to the number of equivalents used. [c] Based on starting olefin. [d] Adduct heated in benzene/D_2O at 140 °C for 10 h (sealed tube). [e] Registry no.: 4104-47-6. [f] Registry no.: 40866-96-4.

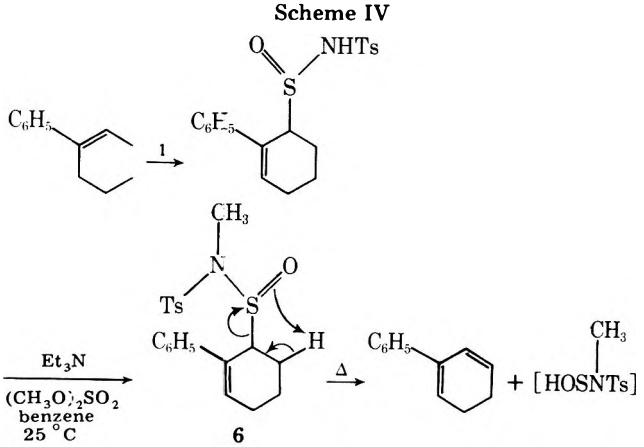
was produced in the retroene process. However, the validity of this assumption was challenged by the following experiment: under the same conditions described above, the T_2O was replaced with 0.1 mL of D_2O and this gave α-methylstyrene which was 25% d_0, 40% d_1, 22% d_2, and 10% d_3. Apparently, under these conditions (much less water than is usually employed), the ene and retroene reactions are occurring several times over before the *N*-sulfinylsulfonamide (TsN=S=O) is hydrolyzed.

Although this single example of allylic tritiation was performed using an isolated sulfinamide adduct, the in situ method (in which the adduct is formed in benzene and then D_2O or T_2O is added directly to the solution of the crude adduct in benzene) is much simpler and should be preferable in most cases where allylic tritiation is desired. We have found that the sulfinamide adducts are often too unstable to isolate. Moreover, if one wished to allylically tritiate a few micrograms of olefin, isolation of the adduct would not be feasible.

One consequence of the ene/retroene mechanism is the loss of stereochemistry in the case of di- and trisubstituted olefins. For example, reaction of either *cis*- or *trans*-5-decene with 1 followed by hydrolysis afforded the same mixture of 23% *cis*- and 77% *trans*-5-decene. Similar results were found for (*Z*)- and (*E*)-3-methyl-2-hexene (the recovered olefin in both cases was 33% (*Z*) and 67% (*E*)). Control experiments showed the olefins were stable (no cis–trans isomerization) to the conditions of the retroene–hydrolysis procedure.

If a suitable β-hydrogen is available, a side reaction involving syn elimination of the allylic sulfinamide group to a diene sometimes competes with the retroene reaction. The yield of diene was generally less than 15%. However, diene formation can be made the exclusive event by obstruction of the retroene pathway through alkylation of the nitrogen of the intermediate allylic sulfinamides. As a particular example (Scheme IV), pyrolysis (by GLPC injection) of the *N*-methylsulfinamide derivative **6** (obtained in only 26% yield) from 1-phenylcyclohexene gave a 90% yield of 2-phenyl-1,3-cyclohexadiene and none of the isomeric diene.[14] Similarly, cyclooctene and (*E*)-5-decene were transformed to 1,3-cyclooctadiene and 4,6-decadiene, respectively.[15a] This sequence

Scheme IV



effects symmetrical (i.e., Δ^2-olefin → $\Delta^{1,3}$-diene) dehydrogenation of an olefin to a conjugated diene, but this new diene synthesis is limited by the fact that the *N*-methylsulfinamide adducts are generally formed in poor overall yield.[15b] In contrast to allylic sulfoxides,[16] these derivatives have given no indication of undergoing 2,3-sigmatropic rearrangement.[17]

In summary, the reversible ene reaction of *N*-sulfinylsulfonamides represents a convenient procedure for the allylic deuteration and tritiation of certain alkenes.

Experimental Section

All mass spectra were collected using a Hitachi Perkin-Elmer RMU-6E mass spectrometer and the percentage of deuterium incorporation was calculated using standard techniques[18] including corrections for natural abundance. Kugelrohr distillation refers to bulb-to-bulb distillation using a Büchi kugelrohr apparatus. The temperatures reported are the air bath temperatures at which the material distilled and are not the true boiling points.

***N*-Sulfinyl-*p*-toluenesulfonamide (1). A.** This procedure is a slightly modified version of Kresze's.[8,20] In a 2.0-L round-bottomed flask fitted with a reflux condenser and a $CaCl_2$ drying tube, a mixture of 250 g of *p*-toluenesulfonamide (1.46 mol, Eastman Organic Chemicals) and 200 g of thionyl chloride (1.68 mol) in 1.0 L of dry benzene was heated for 5 days at reflux. After cooling to room temperature the solvent and excess $SOCl_2$ were evaporated, first at aspirator pressure, then under high vacuum, to leave approximately 300 g of dark orange oil. Kugelrohr distillation in three 100-g portions gave a total of 196 g of 1 (130–140 °C, 0.06 Torr, 62%) which crystallized upon standing to a bright yellow solid, mp 47–51 °C (lit.[8] mp 53 °C).

B. Addition of 1% *N,N*-dichloro-*p*-toluenesulfonamide[21] decreased the time needed for completion. For example, the reaction of 125 g of $TsNH_2$ (0.73 mol) and 173 g of thionyl chloride (1.46 mol) in 100 mL of benzene at reflux (using a $CaCl_2$ drying tube as above) was complete in only 16 h. Evaporation followed by kugelrohr distillation as above gave 1 in 69% yield. *This modified procedure (B) represents a great saving in time (only 16 h instead of 5 days) with no decrease in yield.* Note also that procedure B employs different proportions of reactants and solvent than procedure A.

***N*-Sulfinylmethanesulfonamide (2).**[19] Following procedure A above, 2 was prepared using 15.5 g of methanesulfonamide (16 mmol) and 14 mL of $SOCl_2$ (19 mmol) in 30 mL of benzene. Kugelrohr distillation (165 °C, 0.02 Torr; lit.[8] bp 80 °C, 10^{-4} Torr) gave 13.9 g (62%) of bright yellow oil.

Reaction of 1 with β-Pinene. To a 100-mL round-bottomed flask under anhydrous conditions containing a solution of 5.4 g of TsNSO (24.9 mmol) in 50 mL of benzene (THF or CH_3CN gave equivalent results) was added, with stirring and cooling (ice bath), 3.6 mL of β-pinene (22.7 mmol). After stirring overnight at room temperature, the solution was concentrated to about one-half of its volume and cooled. The resulting white precipitate was collected and washed with a small amount of hexanes. After drying in vacuo, 7.13 g of 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl-*N*-(*p*-toluenesulfonyl)methylsulfinamide (3) was obtained (89%), mp 137–139 °C: IR (KBr) 3050 (NH), 2920 (CH), 1595, 1375 (SO_2), 1320, 1185, 1165 (SO_2), 1080, 1065, 860, and 815 cm^{-1}; NMR ($CDCl_3$) δ 9.0 (1 H, broad s, exchangeable with D_2O, NH), 7.9–7.2 (4 H, q, aromatic), 5.60 (1 H, broad s, olefinic), 3.55 (2 H, broad s, $-CH_2S$), 2.4 (3 H, s, aromatic $-CH_3$), 2.2 (5 H, m, ring -H), 1.2 (3 H, s, $-CH_3$), 1.0 (1 H, m, bridgehead) and 0.7 (3 H, d, $-CH_3$). Upon standing at room temperature in the solid state, 14 slowly decomposed to β-pinene and a solid residue consisting mostly of $TsNH_2$.

Anal. Calcd for $C_{17}H_{23}NO_3S_2$: C, 57.76; H, 6.56; N, 3.96. Found: C, 57.00; H, 6.90; N, 3.80.

Allylic Deuteration of β-Pinene with TsNSO (1). A solution of 520 mg of TsNSO (2.4 mmol) in 20 mL of benzene was prepared in a 50-mL round-bottomed flask under anhydrous condition. β-Pinene (0.32 mL 2 mmol) was added with stirring. The reaction could be conveniently monitored by GLPC for the disappearance of olefin (after the removal of the adduct by passing an aliquot through a plug of neutral alumina with hexanes). When the reaction was complete (6 h), 2 mL of D_2O (>99.7% isotopic purity, obtained from Merck Sharp & Dohme, Ltd.) was added to the flask. After stirring at room temperature for 15 min while fitting the flask with a reflux condenser, the mixture was heated (oil bath at 90 °C) for 12 h (after which time no adduct remained by TLC). The benzene layer was separated and passed through a short column of silica gel (30 g) with hexanes (50 mL). The resulting solution was concentrated to leave 190 mg of crude product which was kugelrohr distilled (90–100 °C, water aspirator pressure) to give 162 mg of *trans*-3-deuterio-β-pinene (59%): NMR ($CDCl_3$) δ 4.5 (2 H, m, $=CH_2$), 2.35 (3 H, m, ring H), 1.9 (3 H, m, ring H), 1.4 (1 H, d, bridgehead H), 1.25 (3 H, s, $-CH_3$) and 0.7 (3 H, s, $-CH_3$). Mass spectral analysis showed the deuterated β-pinene to be 14% d_0 and 86% d_1.

Allylic Deuteration of *l*-Carvone Using TsNSO. A mixture of 1.0 g of *l*-carvone (Aldrich, 6.66 mmol, $[\alpha]^{25}_D$ −55.6° (c 8.65, EtOH)) and 2.89 g of TsNSO (13.3 mmol) was stirred in 20 mL of benzene in a 50-mL round-bottomed flask (anhydrous conditions) for 24 h. GLPC showed no olefin remaining, so 12 mL of D_2O (>99.7% *d*) was added and the mixture refluxed for 7.5 h. The reaction was cooled, taken up in ether which was washed once with H_2O and once with brine, and dried. Filtration and evaporation left 700 mg of crude oil which was kugelrohr distilled (50–70 °C, 0.5 Torr) to give 450 mg of deuterated *l*-carvone contaminated with approximately 5% dehydrocarvacrol. Pure *l*-carvone, isolated by preparative GLPC (8 ft × ¼ in. 20% SE-30 on 45/60 mesh Chromsorb W, 150 °C) was 13% d_0, 46% d_1, 35% d_2 and 6% d_3, and showed little change in optical rotation ($[\alpha]^{25}_D$ −54.7° (c 8.45, EtOH)).

The excess deuterium was exchanged by heating the crude deuterated *l*-carvone (250 mg) in 5 mL of 60% EtOH containing 3 drops of 50% NaOH solution at 50–60 °C for 3 h in a 25-mL round-bottomed flask under N_2. Extraction with hexane (washed once with H_2O and once with brine, and dried) followed by evaporation gave 240 mg of yellowish oil which was kugelrohr distilled to give 230 mg of 10-deuterio-*l*-carvone (90%, 39% overall): NMR ($CDCl_3$) δ 6.75 (1 H, m, olefinic), 4.7 (2 H, broad s, $=CH_2$), 2.5 (5 H, m, ring H) and 1.75 (5 H, two overlapping s, $-CH_3$ and $-CH_2D$). A pure sample of 10-deuterio-l-carvone was collected by preparative GLPC: 16% d_0, 82% d_1, and 2% d_2, $[\alpha]^{25}_D$ −55.0° (c 9.45, EtOH).

Allylic Tritiation of α-Methylstyrene. In a dry 25-mL round-bottomed flask fitted with a reflux condenser and $CaCl_2$ trap, a mixture of 670 mg of *N*-(*p*-toluenesulfonyl)-2-phenyl-2-propenylsulfinamide[6] (2 mmol, recrystallized from $CHCl_3$ and dried in vacuo) and 0.1 mL of 1 Ci/mL T_2O (100 mCi) in 5 mL of benzene was refluxed for 14 h. After cooling, 5 mL of pentane was added and the organic phase eluted through a 7.0 × 0.5 cm silica gel column with an additional 5 mL of pentane (this removes the T_2O and the *p*-toluenesulfonamide). The resulting solution was concentrated to afford 120 mg of an oil which was kugelrohr distilled (80–90 °C, water aspirator pressure) to give 110 mg (49%) of tritiated α-methylstyrene: specific radioactivity = 1.78×10^6 dpm/μmol or 0.8 μCi/μmol; GLPC analysis (6 ft × 0.125 in. OV-17 on 80/100 mesh Gas Chrom Q, 70 °C) showed only one peak which coinjected with an authentic sample. Redistillation of the product caused no change in the specific activity. The original 100 μL of T_2O contained about 11 mmol of protons and another 2 mmol of protons were introduced with the sulfinamide adduct. Thus the 100 mCi of activity was distributed over 13 mmol of protons resulting in a specific activity for the reaction medium of 7.7 mCi/mmol of H^+. The activity of the α-methylstyrene was 0.8 Ci/mmol, which represents incorporation of tritium into the sample at a specific radioactivity 10% that of the reaction medium (based on replacement of one allylic hydrogen). Replacement of T_2O by 0.1 mL of D_2O under identical conditions and workup gave α-methylstyrene which was 25% d_0, 40% d_1, 22% d_2, and 10% d_3.

2-Phenylcyclohex-2-enyl-*N*-methyl-*N*-(*p*-toluenesulfonyl)sulfinamide. In a 50-mL round-bottomed flask with a magnetic stirrer, under anhydrous conditions, 3.25 g of TsNSO (15 mmol) was added to a solution of 1.0 g of 1-phenyl-1-cyclohexene (6.3 mmol, Aldrich Chemical Co.) in 20 mL of benzene. After 36 h, the reaction mixture was cooled in a refrigerator for approximately 1 h. The resulting precipitate was collected by suction filtration (washed with 25 mL of dry pentane) and dried (1.90 g, 80% yield of 2-phenylcyclohex-2-enyl-*N*-(*p*-toluenesulfonyl)sulfinamide). This solid (5 mmol) was suspended in 40 mL of benzene and 0.80 mL of Et_3N (5.7 mmol) was added followed by 0.6 mL of dimethyl sulfate (96.3 mmol). After 2 h at room temperature, the reaction was taken up in ether which was washed twice with H_2O, once with brine, and dried. Filtration and evaporation left 0.96 g of a white solid which was purified by column chromatography (25 g of silica gel, packed with hexane and eluted with 100 mL: hexanes, 5%; EtOAc/hexanes, 10%, 15%; 10-mL fractions). Concentration of the appropriate fractions gave 0.52 g (26%) of the *N*-methyl adduct (recrystallized from EtOAc/hexanes), mp 160–161 °C (decomposition with evolution of gas), R_f = 0.47 (35% EtOAc/hexanes), not very soluble in ether, benzene, or EtOAc: IR ($CHCl_3$) 2940, 1595, 1490, 1445, 1360 (SO_2), 1305, 1165 (SO_2), 1090, 900, and 890 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.9 (4 H), 4.15 (1 H, broad s, R_2CHS), 2.4 (6 H, s, aromatic $-CH_3$ and NCH_3, addition of shift reagent causes splitting into 2 singlets in ratio of 2:1) and 2.4–1.8 (6 H, m, ring H).

Anal. Calcd for $C_{20}H_{23}NO_3S_2$: C, 61.67; H, 5.95; N, 3.60. Found: C, 61.56; H, 5.98; N, 3.64.

Pyrolysis of 2-Phenylcyclohex-2-enyl-*N*-methyl-*N*-(*p*-toluenesulfonyl)sulfinamide. Injection of a 25% solution of the N-methyl adduct in CH_3OH directly into the gas chromatograph (injection port temperature 250 °C) gave (by area %) 6.4% 1-phenylcyclohexene, 3.6% biphenyl, and 90% diene.

The diene was isolated by preparative GLPC (20 ft × ⅜ in. stainless steel, 20% Carbowax 20M on 45/60 mesh Chromsorb W at 200 °C, t_r = 22 min (t_r(biphenyl) = 26.5 min, t_r (1-phenylcyclohexene) = 19 min, collected at liquid N_2 temperatures). The resulting oil was weighed and dissolved in cyclohexane: UV_{max} 279 nm (ε 7500).

Some biphenyl (230 nm) was present. Both 2-phenyl-1,3-cyclohexadiene (276 nm (ε 8140)) and 1-phenyl-1,3-cyclohexadiene (303 nm (ε 13 800)) are known.[14] Not more than 14% of the 1-phenyl isomer can be present in the isolated samples.

Both 1-phenylcyclohexene and biphenyl were identified by coinjection which authentic samples. Biphenyl was isolated and found to be identical (TLC, melting point, and mixture melting point) with an authentic sample.

Acknowledgments. We are grateful to our colleagues, Yak Cheung and Christopher T. Walsh, for assistance with the tritium incorporation experiments. We thank the National Science Foundation (CHE 74-21260) and the National Institutes of Health (GM 21686) for financial support.

Registry No.—*p*-Toluenesulfonamide, 70-55-3; thionyl chloride, 7719-09-7; *N,N*-dichloro-*p*-toluenesulfonamide, 473-34-7; methanesulfonamide, 3144-09-0; *N*-(*p*-toluenesulfonyl)-2-phenyl-2-propenylsulfinamide, 64976-25-6; α-methyl-β-tritriostyrene, 64976-26-7; 1-phenyl-1-cyclohexene, 771-98-2; 2-phenylcyclohex-2-enyl-*N*-(*p*-toluenesulfonyl)sulfinamide, 64976-27-8; 2-phenylcyclohex-2-enyl-*N*-methyl-*N*-(*p*-toluenesulfonyl)sulfinamide, 64976-28-9; biphenyl, 92-52-4; 2-phenyl-1,3-cyclohexadiene, 15619-34-8; 1-phenyl-1,3-cyclohexadiene, 15619-32-6.

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Aliphatic Azoxy Compounds. 7. Unsymmetrical (Dialkoxymethyl)phenyldiazenes: Deoxygenation of an Azoxy Function[1]

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In an investigation of the reactivity of the biologically important distal carbon atom of a model azoxyalkane, we observed that **1a** was converted, in good yield, to phenyldimethoxymethyldiazene (**2a**).[2] We wanted to know if the reaction conditions permitted the incorporation of two different alkoxyl group nucleophiles into **2** or if alkoxyl group interchange (e.g., via addition to tautomer **3**[3]) would prevent this. In so doing we wanted to learn more about the scope of this reaction for the synthesis of compounds **2**, an unusual, and new, class of azo compound. Herein we report on the preparation, stability, and spectral properties of **2b–d**, results which apply in a practical way to the questions raised above.

The starting azoxy compound **1c** was prepared by the procedure used previously for **1a,b,d**.[2] Compounds **1b–d** were smoothly converted to liquids **2b–d** by treatment with triethylamine in methanol at 25 °C in the presence of a drying agent (see Scheme I). Conversion of **1** to **2** was 95–98% complete as determined by VPC; isolated yields of 49–58% of 98% pure **2** were obtained after silica gel chromatography. Diazene **2c** was prepared in comparable yield by alternate routes starting with **1a** in 1-propanol and using triethylamine or potassium hydroxide as bases. Diazene **2c** was stable for more than 1 day in refluxing 0.05 N aqueous methanolic potassium hydroxide solution, conditions expected to hydrolyze hydrazone **3** should it be formed in situ. In contrast, **2c** was quickly destroyed in 0.03 N hydrochloric acid at room temperature.

Scheme I

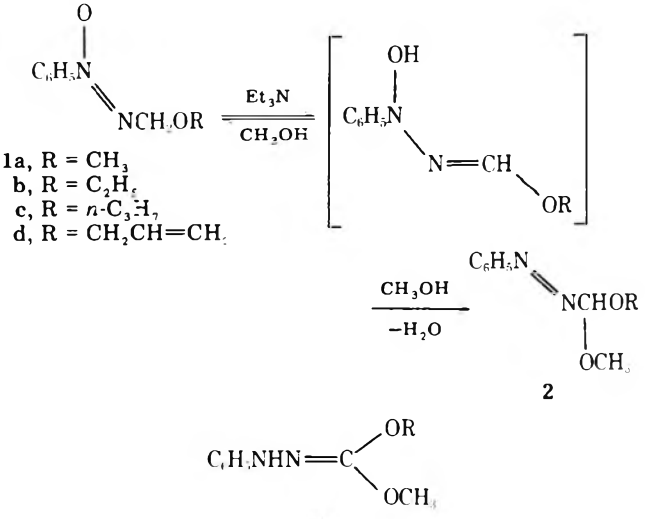

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Table I. Spectral Features of (Dialkoxymethyl)phenyldiazenes 2[a]

Compd	Registry no.	R	^{1}H chemical shift, δ (Me_4Si) CH	OCH_3	α	β	γ	UV λ_{max} (EtOH), nm (log ε)
2b[b]	65102-03-6	$-CH_{2\alpha}CH_{3\beta}$	5.09	3.48	3.80[c]	1.19		269 (3.92), 215 (3.95)
2c[d]	65102-04-7	$-CH_{2\alpha}CH_{2\beta}CH_{3\gamma}$	5.02	3.53	3.72[c]	1.63	0.95	268 (3.96), 215 (4.01)
2d[b]	65102-05-8	$-CH_{2\alpha}CH_{\beta}{=}CH_{2\gamma}$	5.18	3.55	4.38	5.0–5.4	5.6–6.2	269 (3.92), 214 (4.02)

[a] All compounds showed NMR absorptions at δ 7.7 for *o*-Ph and at δ 7.5 for *m*- and *p*-Ph protons; IR absorptions included those at 1520 (medium, $\nu_{N=N}$), 1120 and 1060 cm^{-1} (strong, ν_{CO} acetal). [b] NMR solvent: acetone-d_6. [c] Diastereotopic splitting of the expected multiplet was observed. [d] NMR solvent: CCl_4.

The structures of **2b–d** are based on their elemental analyses and the spectral data gathered in Table I. The spectral features which distinguish the diazenes **2** from a possible (tautomeric) hydrazone structure are (1) the chemical shift of the methylidyne H, δ 4.9–5.2 (vs. δ >6.5 for the usually broad phenylhydrazone NH[4]), (2) the value of the UV extinction coefficient (ε) for the 260–280-nm absorption of phenylalkyldiazenes near 10 000[5] (vs. 18 000–20 000 for the similar absorption of phenylhydrazones[6]), and (3) the absence of NH stretch in the IR spectra of **2** (vs. ν_{NH} of 3300–3450 cm^{-1} for hydrazones[6]).

The conversion of **1** to **2**, analogous to the conversion of di(1-butyl)diazene oxide to 1-butyl-2-pentyldiazene by methyllithium,[7] joins the growing list of selective transformations which can be effected at both distal[2] and proximal[8] carbon atoms of azoxyalkanes.

Experimental Section

General. For instruments used see the Experimental Section of ref 2. VPC analyses were performed using the following aluminum tubing columns: A, 4 ft × 0.25 in. 10% SE-30 on Chromosorb W (AW and DMCS); B, 6 ft × 0.25 in. 5% silicone oil Dow 710 on Chromosorb W (AW and DMCS); C, 6 ft × 0.125 in. 5% UCW 98 on Diatoport S. Dialkyldiazene oxides are animal carcinogens. However, phenylhydroxymethyldiazene 1-oxide (**1**, R = H) produced no tumors in rats at dose levels which with dimethyldiazene oxide produced tumors with 100% frequency.[9]

(*Z*)-Phenylpropoxymethyldiazene 1-Oxide (1c). The title compound was prepared in 85% yield using the silver carbonate procedure described in ref 2. Preparative VPC (column A) provided an analytical sample: NMR ($CDCl_3$) δ 8.12 (m, 2 H, *o*-Ph), 7.4 (m, 3 H, *m*- and *p*-Ph), 5.15 (s, 2 H, distal CH_2), 3.62 (t, 2 H, OCH_2), 1.71 (m, 2 H, CCH_2), 0.97 (t, 3 H, CH_3); IR (neat) 1490, 1425, 1355, and 1325 cm^{-1}; UV λ_{max} (95% C_2H_5OH) 247 nm (ε 10 500). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27. Found: C, 61.61; H, 6.98.

(*E*)-(Methoxyethoxymethyl)phenyldiazene (2b).[10] A mixture of 0.560 g (3.1 mmol) of **1b**, 0.50 g of triethylamine, 0.50 g of magnesium sulfate, and 0.25 g of calcium sulfate in 7 mL of methanol was stirred 1 day at room temperature. After filtration and concentration in vacuo the resulting red oil was chromatographed over 30 g of silica gel. Elution with benzene gave 0.30 g (50%) of 95% pure **2b** as a red oil. Preparative VPC using column B gave an analytical sample. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.74. Found: C, 62.00; H, 7.38.

(*E*)-(Methoxypropoxymethyl)phenyldiazene (2c). This compound was prepared from **1c** and methanol in 58% yield, 98% pure, by the method described for **2b**. Preparative VPC on column A gave an analytical sample. Alternately, **2c** was prepared in similar yield from **1a** and 1-propanol using triethylamine as base and from **1a**, 1-propanol, and 0.2 mol equiv of 1 N KOH. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74. Found: C, 63.22; H, 7.57.

(*E*)-(Methoxy-2-propenoxymethyl)phenyldiazene (2d). This compound was prepared from **1d** in 49% yield by the method used to make **2b**. Preparative VPC using column B gave an analytical sample. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 63.88; H, 6.78.

Stability Studies. A solution of 0.10 g of **2c** in 0.5 mL of 0.1 N aqueous hydrochloric acid and 1.0 mL of methanol was stirred at room temperature. VPC analysis (column C) after 1 h showed no trace of **2c**.

VPC analysis (column C) of a solution of **2c** in 0.5 mL of methanolic 0.1 N KOH and 0.5 mL of water showed no loss of **2c** after 1 day at reflux and 10% loss of **2c** after 6 days at reflux.

Registry No.—**1b**, 57496-83-0; **1c**, 65102-06-9; **1d**, 57496-85-2; methanol, 67-56-1.

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An Improved Method for the Synthesis of Stabilized Primary Enamines and Imines

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Primary β-enamino carbonyl compounds are interesting as potential intermediates in the synthesis of natural and synthetic compounds possessing biological activity. They are rendered especially versatile by their reactivity at both nitrogen and the α carbon, with the possibility existing of systematically directing reaction at either site.[1] Established syntheses of these compounds proceed from the corresponding β-dicarbonyl compound using ammonia[2] or a synthetic equivalent of ammonia[3] to form the enamine. Although these methods are useful, both lack generality when dealing with multifunctional compounds which are sensitive to the strongly basic and nucleophilic reagents required by each. Thus, the Dieckmann–Prelog method[2] (direct treatment with ammonia) is time consuming and apparently limited to structurally simple β-keto esters.[3] The Takaya method,[3] while more general in scope, requires in its second step the use of sodium ethoxide in refluxing ethanol, conditions which are often destructive to other moieties in a potential substrate, particularly exchangeable esters.

This note describes a new method for effecting this transformation which uses a markedly less nucleophilic reagent and proceeds under acid catalysis. *N*-Trimethylsilyliminotri-

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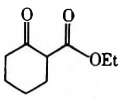
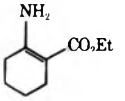
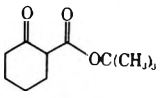
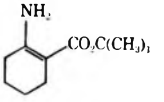
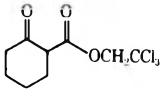
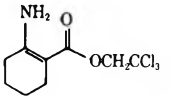
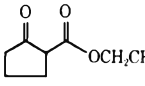
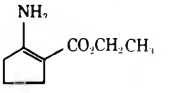
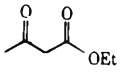
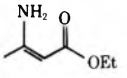
Table I[a]

Entry	Starting material	Registry no.	Product	Registry no.	Yield,[b] %	Bp, °C (mmHg) [mp]
1		1655-07-8		1128-00-3	88	[70–72]
2		55623-56-8		65277-17-0	68	80–90 (15)
3		65277-16-9		65277-18-1	43	135 (0.05) (KR)
4		611-10-9		7149-18-0	91	[58–59]
5		141-97-9		7318-00-5	73	[33–35]
6		123-54-6		1118-66-7	68	110–115 (10)
7		2816-57-1		13652-33-0	40	65–75 (12)

[a] All compounds listed had physical and spectral properties consistent with those in the literature or satisfactory elemental analysis. [b] Yields represent isolated material and have not been maximized in all cases.

phenylphosphorane (I) (easily prepared from triphenylphosphine and azidotrimethylsilane[4]) reacts with β-dicarbonyl compounds (II) in the presence of a molar equivalent of a secondary alcohol and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding β-amino-α,β-unsaturated carbonyl compounds (III). The results are summarized in

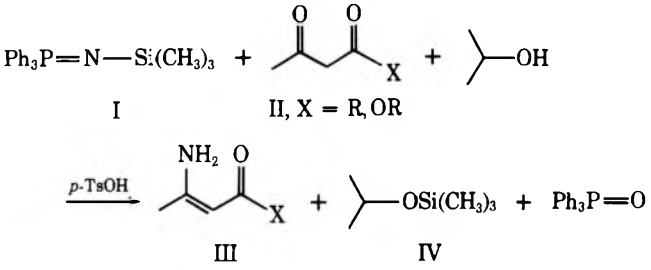


Table I. As can be seen from entry 7, the reagent also forms unconjugated imines, providing they are stable to the reaction conditions. Particularly noteworthy is the lack of ester exchange in the β-keto esters.

The observation that no reaction takes place in the absence of the alcohol suggests that the method proceeds by in situ generation of iminotriphenylphosphorane.[5] Thus the initial step is cleavage of the nitrogen–silicon bond to form the unprotected iminophosphorane and the corresponding trimethylsilyl alkoxide IV.[6] Condensation with the ketone then follows, affording the desired product III and triphenylphosphine oxide. Credence to this mechanism is lent by the report that iminotriphenylphosphorane itself undergoes a similar condensation with certain exceptionally reactive ketones.[5,7]

The principal limitation seems to be the stability of the product to the reaction conditions. Thus, when the sequence was employed with cyclohexanone, the ketone was consumed and triphenylphosphine oxide was produced, but no volatile products were found. Presumably the imine was formed and then underwent random selfcondensation.

In summary, the method described has the following advantages. It allows for the rapid, one-step conversion of appropriate ketones to their corresponding primary enamines or imines. It is the only method available for effecting this conversion without the use of strong bases and/or nucleophiles, thus allowing synthesis of a wider variety of target molecules, particularly those containing exchangeable esters. Lastly, the reagent is easily synthesized and can be readily manipulated without fear of atmospheric hydrolysis.

Experimental Section

General Procedure for the Condensation of *N*-Trimethylsilyliminotriphenylphosphorane (I) with Ketones. To a solution of 1 molar equiv each of the desired keto compound, isopropyl alcohol, and I in a convenient amount of benzene was added a catalytic amount of *p*-toluenesulfonic acid. The resulting solution was refluxed until the reaction was complete (4–8 h). The solution was cooled, concentrated on a rotary evaporator, and diluted with ether. The resulting precipitate of triphenylphosphine oxide was removed by filtration, and the filtrate was concentrated again. The resulting crude product was purified by distillation.

Registry No.—I, 13892-06-3.

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(7) While one could picture iminotriphenylphosphorane itself effecting the transformation described here, its experimental use proves to be less than ideal. Since simple exposure to the atmosphere results in hydrolysis to ammonia and triphenylphosphine oxide, rigorously anhydrous conditions are required for its synthesis, storage, and use. Reactions of this reagent with other than the most highly reactive of ketones are thus often complicated by decomposition of the reagent. In contrast, the trimethylsilyl-protected compound employed here is stable to atmospheric moisture and requires no undue care in its manipulations.

Studies in the (+)-Morphinan Series. 4.[1] A Markedly Improved Synthesis of (+)-Morphine

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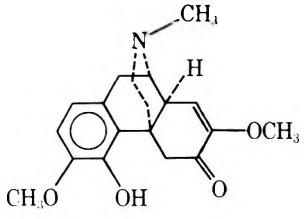
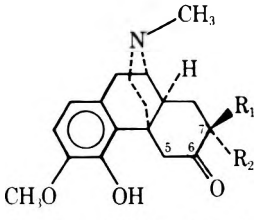
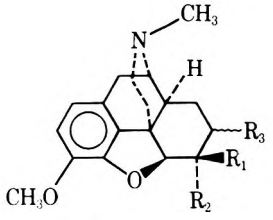
The absolute configuration of the morphinan skeleton of (−)-sinomenine (**1**)[3] is enantiomeric to natural (−)-morphine, and conversion of **1** into (+)-morphine (**10**) was reported by



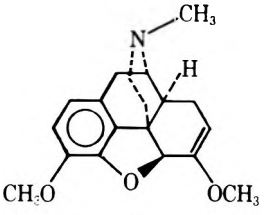
1



2a, $R_1 = OCH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = OCH_3$



3, R_1, $R_2 = O$; $R_3 = H$
4, $R_1 = R_2 = OCH_3$; $R_3 = H$
6, $R_1 = R_2 = OCH_3$; $R_3 = Br$



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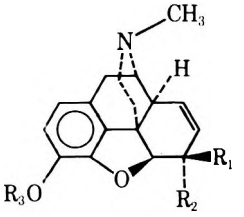

7, $R_1 = R_2 = OCH_3$; $R_3 = CH_3$
8, R_1, $R_2 = O$; $R_3 = CH_3$
9, $R_1 = OH$; $R_2 = H$; $R_3 = CH_3$
10, $R_1 = OH$; $R_2 = R_3 = H$
11, $R_1 = OAc$; $R_2 = H$; $R_3 = Ac$

Goto's group.[4a-c] To define morphine's interaction with opiate receptors more clearly,[5] we wanted to prepare large quantities of unnatural enantiomer **10** and several of its congeners. We now summarize our results that followed, in principal, Goto's original scheme,[4a-c] but which implemented novel reactions and the findings of others, especially those of Rapoport et al.[6] Rapoport's results in the natural (−) series became available only after we had started our project. A tenfold increase in the overall yield of (+)-morphine (**10**), previously reported by Goto, from (−)-sinomenine (**1**) was accomplished as follows.

Catalytic reduction[7] of **1** afforded a mixture of two diastereomers (**2a** and **2b**) which was separated by preparative thin-layer chromatography. The equilibrium mixture was reestablished by brief boiling of either isomer in methanol. Deuterium exchange of **2a** and **2b** allowed definitive assignment of the chemical shift of the C-5 and C-7 protons. Assuming that the preferential conformation of ring C is the chair form, the absolute configuration of **2a** and **2b** at C-7 could be determined. Major isomer **2a** and minor isomer **2b** were assigned 7*R* (axial H) and 7*S* (equatorial H) configurations, respectively, for the following reasons. The chemical shift of the C-7 equatorial proton, due to the shielding effect of the carbonyl group in the 7*S* isomer, lies upfield of the C-7 axial proton in the 7*R* isomer, in accord with previous work on α-methoxydecalones.[8] The chemical shift of the C-7 proton of the 7*S* isomer was δ 3.36 (t, J = 3.5 Hz) and that of the C-7 proton in the 7*R* isomer was δ 3.90 (center of d of d, J = 7, 12 Hz), and the coupling constants were of the magnitude expected. The equatorially oriented C-7 methoxyl group in the 7*R* isomer was deshielded by the carbonyl group (δ 3.43), as compared with the methoxy group in the 7*S* isomer (δ 3.30), again in accord with α-methoxydecalones.[8] Molecular models (Dreiding) indicate that the major product might well be the 7*R* isomer because of the less sterically hindered methoxyl group. The C-5 equatorial proton in both 7*R* and 7*S* isomers was considerably deshielded, presumably due to its proximity to the aromatic ring (see Experimental Section). A similar effect was noted in dihydrothebainone.[6]

Since the next step, the acid-catalyzed S_N2' cyclization of **2a** and **2b** to **3**, with loss of methanol, proceeds under conditions which equilibrate the two epimers, the mixture was treated directly with polyphosphoric acid at 65–70 °C. Ketone **3** is rather stable under these reaction conditions, in contrast to Goto's[9] more drastic conditions; and yields of desired ketone **3** were consistently 70–75%.

Introduction of a double bond in the 7,8 position of **3** is not easy, and attempts to introduce it by direct oxidation were unsuccessful. This could, however, be accomplished by phenylselenation and oxidative elimination, but only after the *N*-methyl group was replaced by a *N*-carbethoxy group.[10] Meanwhile, Rapoport's modification for converting (−)-dihydrocodeinone (enantiomer of **3**) into (−)-codeinone (enantiomer of **8**) became known[6] and was successfully implemented in our plan, which now took the following course: ketalization of **3** to dimethyl ketal **4** (98%); elimination of methanol with *p*-toluenesulfonic acid in chloroform to give enol methyl ether **5** (83%); addition of methyl hypobromite, leading to bromodimethyl ketal **6** (75%); elimination of HBr with potassium *tert*-butoxide in Me_2SO at room temperature instead of 60 °C[6] to give **7** (87%); and deketalization of **7** with 5% HCl instead of AcOH[6] to give (+)-codeinone (**8**; 96%).

Compounds **3** and **5–8** showed the properties previously reported by Goto et al., and **3–8** had properties identical with the corresponding compounds in the (−) series prepared as described by Rapoport,[6] except for the optical rotation. Reduction of unsaturated ketone **8** with sodium borohydride in methanol[11] afforded (+)-codeine (**9**), which was converted into (+)-morphine (**10**) by O-demethylation[12] with boron tribromide in chloroform. Unknown (+)-heroin (**11**) was obtained from **10** by treatment with acetic anhydride. Crystallization from ethyl acetate gave prisms identical with authentic (−)-heroin (enantiomer of **11**), except for the sign of optical rotation. (−)-Heroin showed specific optical rotation 10° higher than previously reported.[13]

(+)-Codeine (**9**), (+)-morphine (**10**), and (+)-heroin (**11**) showed no analgesic activity on subcutaneous injection in mice in routine screening for centrally active analgesics. Unnatural

(+)-morphine (**10**) showed interesting central effects when injected intracerebrally in rats, suggesting the existence of multiple morphine receptors in the brain.[14]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this Laboratory. The identity and chemical purity of **3**–**11** were confirmed by direct comparison with authentic samples of the enantiomeric (−) series. IR, NMR (using tetramethylsilane at δ 0.0 as an internal reference), and mass spectra were obtained on Perkin-Elmer 257, Varian Model HR-220, and Hitachi RMU-6E (70 eV) instruments, respectively. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Silica gel GF plates for analytical and preparative TLC were purchased from Analtech, Inc., Newark, Del.

7(*R*)- and 7(*S*)-(+)-Dihydrosinomenine (2a and 2b). Sinomenine (**1**; 16.6 g, 50.40 mmol) was dissolved in MeOH (450 mL) and hydrogenated using 10% Pd/C as a catalyst until the absorption of hydrogen stopped at approximately 1 mol. After filtration of the catalyst, the solvent was evaporated to give an oil residue which solidified on the addition of ether (200 mL), and the product was collected by filtration. This product (16.5 g) melted at 190–195 °C (lit.[7] mp 198 °C) and was used for conversion to **3** without further purification. Preparative TLC of a portion (150 mg) of this mixture of position 7 epimers over silica gel GF (Et_2O–MeOH, 9:1) gave as the major component the lower R_f 7*R* epimer (100 mg, 67%), which showed, after crystallization from $CHCl_3$–Et_2O (1:10), mp 196.5–197.5 °C; $[\alpha]^{23}_D$ +121° (c 1.28, $CHCl_3$); IR ($CHCl_3$) 1733 cm^{-1}; NMR ($CDCl_3$) δ 6.60 (2 H, AB system, J = 8 Hz, aromatic H), 6.44 (1 H, brd s, OH), 4.30 (1 H, d, J = 13 Hz, C-5 equatorial H), 3.90 (1 H, dd, J = 7, 12 Hz, C-7 axial H), 3.80 (3 H, s, aromatic OCH_3), 3.43 (3 H, s, C-7 OCH_3), 2.41 (3 H, s, N-CH_3), 2.25 (1 H, d, J = 13 Hz, C-5 axial H).

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.04; H, 7.54; N, 4.18.

The higher R_f 7*S* epimer (39 mg, 26%) was obtained as the minor isomer and showed, after crystallization from $CHCl_3$–Et_2O (1:10), mp 196.5–197.5 °C; $[\alpha]^{23}_D$ +87° (c 1.49, $CHCl_3$); IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 6.64 (2 H, dd, J = 8 Hz, aromatic H), 6.26 (1 H, brd s, OH), 4.07 (1 H, d, J = 13 Hz, C-5 equatorial H), 3.82 (3 H, s, aromatic OCH_3), 3.36 (1 H, t, J = 3.5 Hz, C-7 equatorial H), 3.30 (3 H, s, C-7 OCH_3), 2.73 (1 H, d, J = 13 Hz, C-5 axial H), 2.42 (3 H, s, N-CH_3).

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.08; H, 7.54; N, 4.13.

(+)-Dihydrocodeinone (3). The mixture of **2a** and **2b** from above (3.00 g, 9.05 mmol) and polyphosphoric acid (Matheson, Coleman and Bell, 60 g) was heated at 65–70 °C for 1.25 h while stirring. The cooled reaction mixture was basified by the careful addition of ammonium hydroxide (28%) at 0 °C, saturated with NaCl, and extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and evaporated to afford a solid, which was recrystallized from Et_2O–$CHCl_3$ (3:1) to give **3** (1.98 g, 73%): mp 196.5–197.5 °C (lit.[9] mp 197–198 °C); $[\alpha]^{23}_D$ +205.3° (c 0.9, $CHCl_3$) [lit.[9] $[\alpha]_D$ +207.4° ($CHCl_3$)].

Conversion of (+)-Dihydrocodeinone (3) to (+)-Codeine (9). (+)-Codeine (**9**) was prepared from (+)-dihydrocodeinone (**3**) essentially as described by Rapoport[6] in the (−) series via the following intermediates. (+)-Dihydrocodeinone dimethyl ketal **4**: mp 121–122 °C; $[\alpha]^{23}_D$ +167.2° (c 1.1, EtOH) [lit.[15] (−) enantiomer of **4**: mp 122–123 °C, $[\alpha]_D$ −151° (c 0.9, EtOH)]. (+)-8,14-Dihydrothebaine (**5**): mp 162–163 °C; $[\alpha]^{23}_D$ +268.6° (c 1.1, C_6H_6) [lit.[4c] mp 162–163 °C, $[\alpha]_D$ +268.2° (c 1.544, C_6H_6)]. (+)-7-Bromodihydrocodeinone dimethyl ketal **6**: mp 116–117 °C; $[\alpha]^{23}_D$ +165.1° (c 1, $CHCl_3$) [lit.[4c] mp 117 °C, $[\alpha]_D$ +164.5° (c 1.536, $CHCl_3$)]. Treatment of **6** with potassium *tert*-butoxide at 25 °C (48 h) instead of 60 °C[6] gave (+)-codeinone dimethyl ketal **7**: mp 135–136.5 °C; $[\alpha]^{23}_D$ +238.3° (c 1.2, EtOH) [lit.[4c] mp 138 °C, $[\alpha]_D$ +236° (c 1.016, EtOH)]. Hydrolysis of **7** with 5% HCl (0.5 h, 75 °C) instead of AcOH–H_2O[6] gave (+)-codeinone (**8**): mp 185–186 °C; $[\alpha]^{23}_D$ +204.5° (c 1, EtOH) [lit.[4d] mp 186 °C, $[\alpha]_D$ +206.0° (EtOH)]. Reduction of **8** with $NaBH_4$ in MeOH gave (+)-codeine (**9**): mp 157.5–158.5 °C; $[\alpha]^{23}_D$ +136.2° (c 0.7, EtOH) [lit.[4a] mp 158 °C, $[\alpha]^{25}_D$ +137.4° (c 0.743, EtOH)].

(+)-Morphine (10). To a stirred solution of BBr_3 (6.00 g, 24 mmol) in $CHCl_3$ (70 mL) was added **9** (1.167 g, 3.9 mmol) in $CHCl_3$ (10 mL) at 23–26 °C over a 2-min period, and stirring was continued for 15 min. The reaction mixture was poured into a stirred mixture of ice (32 g) and NH_4OH (28% NH_3, 8 mL) and stirred for 30 min at 0 °C. The crystalline material which formed was filtered, washed with cold $CHCl_3$ and then water, and dried to give **10** (800 mg). The aqueous phase from the filtrate was saturated with NaCl and extracted with $CHCl_3$–EtOH (3:1). The combined extracts were evaporated, and the residue was purified by silica gel thin-layer chromatography using $CHCl_3$–MeOH (8:2) as a solvent to yield **10** (241 mg). Total yield was 88%. Recrystallization from MeOH gave **10**·H_2O as colorless prisms: mp 253–255 °C; $[\alpha]^{25}_D$ −132.1° (c 0.49, MeOH) [lit.[4a] mp 247–248 °C, $[\alpha]^{23}_D$ −132.1° (c 0.383, MeOH)].

Anal. Calcd for $C_{17}H_{19}NO_3$·H_2O: C, 67.30; H, 6.98; N, 4.62. Found: C, 67.47; H, 7.25; N, 4.63.

(+)-Heroin (**11**). A mixture of **10** (285 mg, 1 mmol) and acetic anhydride (2 mL) was heated at 90–100 °C for 4 h. Ether was added to the cooled solution, and the mixture was basified with 10% KOH while cooling. The ether phase was separated, the aqueous phase was extracted with ether, and the combined extracts were dried over Na_2SO_4. The solvent was evaporated to give a solid, which was recrystallized from AcOEt to afford **11** (295 mg, 80%): mp 169–170.5 °C; $[\alpha]^{23}_D$ +176° (c 0.63, MeOH) [lit.[13] (−) enantiomer of **11**: mp 173 °C, $[\alpha]^{25}_D$ −166.4° (c 1.49, MeOH)].

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.97; H, 6.37; N, 3.44.

Acknowledgment. We would like to thank Drs. Mario Aceto, Louis Harris, and Everette L. May, Medical College of Virginia, for their encouragment. The analgesic screening of the compounds mentioned was carried out by Mrs. Louise Atwell of our laboratory. We also thank Dr. Mikio Takeda, Tanabe Seiyaku Research Laboratory, and Dr. Wataru Nagata, Shionogi Seiyaku Research Laboratory, for the generous gifts of (−)-sinomenine used in this work.

Registry No.—**1**, 115-53-7; **2a**, 65120-75-4; **2b**, 65120-76-5; **3**, 64520-24-7; **4**, 65165-95-9; **5**, 65165-96-0; **6**, 65165-97-1; **7**, 65165-98-2; **8**, 65494-91-9; **9**, 64520-25-8; **10**, 65165-99-3; **11**, 65166-00-9.

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Cleavage of Tetrahydrofuran by Lithium Bis(2,6-di-*tert*-butylphenoxy)aluminum Hydride

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The reaction of lithium aluminum hydride ($LiAlH_4$) with 2 or 3 molar equiv of 2,6-di-*tert*-butylphenol (I) at room temperature gives lithium bis(2,6-di-*tert*-butylphenoxy)-aluminum hydride (II; eq 1). This is confirmed in Table I for

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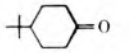
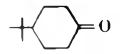
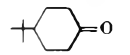
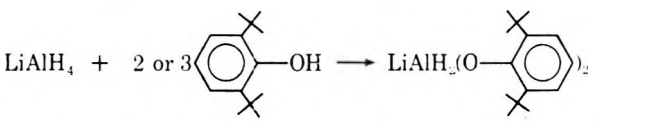
Table I. Reaction of Lithium Aluminum Hydride with Phenols in THF

Entry	$LiAlH_4$, mol	Phenol	Amount, mol	Reflux time, h	Ketone	Amount, mol	% redn	H_2 evol[a]
1	0.010	I	0.020	16				0
2	0.015	PhOH	0.030	19				0.029
3	0.020	I	0.060	16		0.01	0[b]	0
4	0.015	I	0.045	5		0.011	0[c]	0
5	0.015	I	0.045	0		0.01	96[d]	0.013

[a] Moles of H_2 evolved on hydrolysis. [b] Recovered 97% ketone; GLC analysis using 3,3,5,5-tetramethylcyclohexanone as an internal standard. [c] Recovered 93% ketone; GLC analysis using the same internal standard; traces of alcohols present. [d] Alcohol ratio was 53% cis and 47% trans (normalized to 100%).

reactions in tetrahydrofuran (THF), and in each case 2 molar equiv of H_2 are evolved as measured by a wet test meter. A



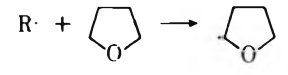
I II

$$+ 2H_2 \quad (1)$$

third 2,6-di-*tert*-butylphenoxy group is difficult to introduce presumably due to steric hindrance.[1,2] On refluxing the clear colorless solutions very little additional H_2 is evolved in the experiments using 3 molar equiv of I,[3] and in all the experiments with I no hydrogen is evolved on hydrolysis with 10% sulfuric acid after the reflux period (Table I, entries 1, 3, and 4). Refluxing of the hydride solutions was carried out under a blanket of nitrogen, although oxygen was not rigorously removed from the system. The absence of hydrogen on hydrolysis implies that no Al–H bonds are present after refluxing, and this was confirmed by the virtual absence of reduction of 4-*tert*-butylcyclohexanone added after the reflux period (Table I, entries 3 and 4). The recovered ketone is unreacted rather than formed by hydrolysis of an enolate as shown by (1) a carbonyl stretching band at 1706 cm^{-1} in the IR spectrum of a reaction mixture sampled prior to hydrolysis, (2) the absence of gas evolution during addition of the ketone, and (3) in an experiment in which $LiAlH_4$ was added to a reaction mixture prior to hydrolysis, the epimeric alcohol ratio was found to be 86% trans and 14% cis, close to that reported for the reduction of 4-*tert*-butylcyclohexanone with $LiAlH_4$ in THF.[4]

On the other hand, in the absence of heating the hydride species II reduces 4-*tert*-butylcyclohexanone in a normal manner, giving 53% cis and 47% trans alcohols with very little residual ketone (Table I, entry 5).

A solution formed by the reaction of $LiAlH_4$ (0.04 mol) with I (0.08 mol) in THF and refluxed for 18.5 h was hydrolyzed with water and sodium hydroxide solution[5] (no H_2 evolution occurred on hydrolysis), and the product was distilled. *n*-Butyl alcohol (0.061 mol) was isolated and identified by IR, NMR, and GLC comparison with an authentic sample. This alcohol undoubtedly was formed from the cleavage of THF by II on heating. The cleavage of THF can be explained by two different mechanisms. One involves radical formation (eq 2) followed by ring opening of the tetrahydrofuranyl radical.[6] Radical cleavage of the THF ring could result in the formation of an aldehyde[7] group which would be reduced by II, thus

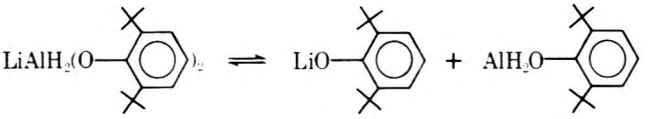


(2)

accounting for the destruction of the Al–H bonds. Assuming that no free I remains after the reaction of 2 molar equiv of I with $LiAlH_4$, the radicals must initially be produced by thermal homolysis of Al–O–C_6H_3-2,6-(t-Bu)$_2$ bonds. Thermal homolysis of an Al–C bond has been observed with diphenyltritylaluminum.[8] In this case a stable triphenylmethyl radical was formed, while in the present example a relatively stable phenoxyl radical would be produced.

A direct attack of the hydride species II on THF via a polar mechanism seems unlikely, although it cannot be ruled out, from a consideration of the markedly different behavior of phenol itself, as shown in Table I, entry 2. After refluxing a THF solution of lithium aluminum diphenoxyhydride (III) for 19 h, acidic hydrolysis produced the calculated quantity of residual hydrogen, and the original number of hydride equivalents in $LiAlH_4$ was quantitatively accounted for. If the sterically hindered reagent II was able to directly attack THF, the less hindered and electronically similar reagent III would be expected to do the same.

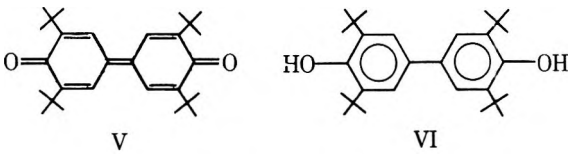
It is conceivable that II exists in equilibrium with a tricoordinate aluminum species IV, as shown by eq 3.[9] Species



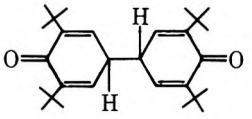
II IV (3)

IV can form a complex with THF, leading to its reduction. If this mechanism is correct, then the formation of IV may be attributed to steric hindrance inherent in species II (as compared with its absence in III).

There is another difference in behavior between phenol and I. With the reagent III the reaction mixture remained clear and colorless before and after heating. In the reactions of I a deep yellow to orange color always developed soon after the reflux period. Small amounts of a dark brown crystalline solid were isolated. Various samples of this material melted fairly sharply between 206 and 209 °C. The solid was shown to be an approximately equimolar mixture of 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (V) and the diphenol VI by NMR, IR, and UV comparison with samples of V and VI prepared independently. Compounds V and VI are probably formed from the phenol I by radical reactions, possibly involving compound VIII as an intermediate.[10] 2,6-Di-*tert*-butylphenoxy radicals can combine through the para positions to form VI.[11] The isolated dark brown crystalline mixture of V and VI is much darker in color than each of the separate components. This may be due to quinhydrone-type complex formation in the solid state. Evaporation of a THF solution of V and VI gave a similar deep brown solid. A quinhydrone complex of the



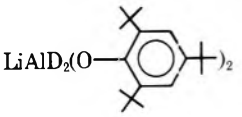
V VI



VII

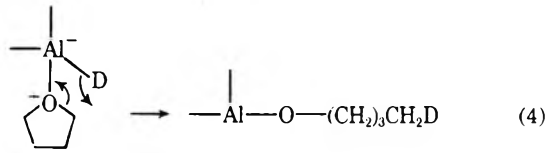
methyl analogues of V and VI (*tert*-butyl groups replaced by methyl) has been reported.[12]

In order to distinguish between the radical mechanism of ring cleavage and a polar mechanism involving a tricoordinate aluminum reagent such as IV, the deuterated reagent VIII was

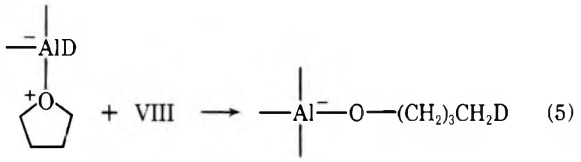


VIII

prepared by the reaction of $LiAlD_4$ with 2,4,6-tri-*tert*-butylphenol[14] in THF. The reaction mixture was refluxed, and following hydrolysis with aqueous base,[5] the deuterated *n*-butyl alcohol was isolated by distillation. Analysis by NMR spectroscopy clearly showed the product to be $CH_2DCH_2CH_2CH_2OH$. Thus, the radical mechanism involving the formation and reduction of an aldehyde is ruled out, and a mechanism involving cleavage by a tricoordinate aluminum species such as IV is supported. The mechanism can either involve intramolecular (eq 4) or intermolecular (eq 5) attack by hydride.



(4)



(5)

The radical reactions leading to products V and VI are apparently unrelated to the cleavage of THF.

Experimental Section

2,6-Di-*tert*-butylphenol (I) was obtained from the Aldrich Chemical Co. and was fractionally distilled through a 12-in helix-packed column, giving a clear colorless distillate, bp 105 °C (8 mm). 2,4,6-Tri-*tert*-butylphenol was purified by recrystallization from aqueous ethanol. Lithium aluminum deuteride was obtained from the Alfa Ventron Corp. 4-*tert*-Butylcyclohexanone was purified by distillation. Tetrahydrofuran was distilled from $LiAlH_4$ through a helix-packed column immediately before use. $LiAlH_4$ solutions in THF were obtained from the Alfa Ventron Corp., and the molarity was checked by measurement of hydrogen evolution on reaction with a phenol–THF solution. GLC analysis was carried out with a Hewlett Packard Model 5750 instrument. NMR analysis was carried out on a Jeol MH-100 instrument.

Preparation of Lithium Bis(2,6-di-*tert*-butylphenoxy)aluminum Hydride (II). A 100-mL three-neck flask with a magnetic stirring bar was flamed under nitrogen, and 10 mL of a 1.0 M $LiAlH_4$–THF solution was added by pipet in a drybox. The flask was then fitted under nitrogen with a reflux condenser and an equilibrated dropping funnel and attached to a wet test meter separated from the flask by a $CaSO_4$ trap. The nitrogen was discontinued, and a solution of the phenol (I; 4.12 g, 0.02 mol) in THF was added dropwise with stirring. After the addition the reaction flask was disconnected from the wet test meter and again placed under a nitrogen atmosphere and heated under reflux (oil bath) for 16 h. On cooling under nitrogen the reaction mixture turned deep yellow. Hydrolysis of the reaction mixture attached to the wet test meter with 10% H_2SO_4 resulted in no gas evolution.

In experiments involving the addition of 4-*tert*-butylcyclohexanone, the reaction mixture was worked up by extracting with ether, washing the organic layer consecutively with saturated $NaHCO_3$ and NaCl solutions, and drying over anhydrous $MgSO_4$. The solutions were concentrated by distillation through a helix-packed column and analyzed by GLC on an 12 ft × ⅛ in 5% Carbowax 20M column at 136 °C after addition of an internal standard.

Preparation of 3,3′,5,5′-Tetra-*tert*-butyldiphenoquinone (V). 2,6-Di-*tert*-butylphenol (I) was oxidized by alkaline ferricyanide according to the procedure of Cook, English, and Wilson.[13] The product consisted of reddish brown needles: mp 245–247 °C (lit. mp 240–241,[12] 246 °C[8]); IR (carbonyl band) 1600 cm^{-1} (s); NMR ($CDCl_3$) δ 1.38 (s, 36 H), 7.66 (s, 4 H).

Preparation of 4,4′-Dihydroxy-3,3′,5,5′-tetra-*tert*-butyldiphenol (VI). The diphenoquinone V (1g, 0.0025 mol) in 20 mL of THF was reduced with 0.01 mol of $LiAlH_4$. Hydrolysis with water and 10% H_2SO_4 gave yellow needles after recrystallization from 95% ethanol: mp 185–187 °C (lit.[8] mp 185 °C); IR (OH stretch) 3610 cm^{-1} (s, sharp); NMR (CCl_4) δ 1.47 (s, *tert*-butyl), 4.92 (s, OH), 7.06 (s, ring H's).

Acknowledgment. The support (to H.H.) of the Faculty Research Award Program, The City University of New York, Grants 11419 and 10193, is gratefully acknowledged.

Registry No.—I, 128-39-2; II, 54004-00-1; V, 2455-14-3; VI, 128-38-1; $LiAlH_4$, 16853-85-3; phenol, 108-95-2; 4-*tert*-butylcyclohexanone, 98-53-3; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-33-5; tetrahydrofuran, 109-99-9.

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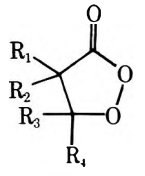
Communications

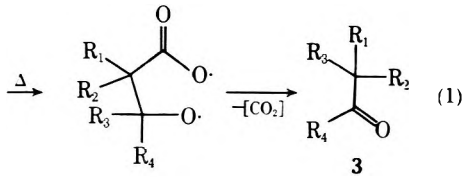
Solvent Effects and Secondary Isotope Effects for Probing Diradical Character in the Thermal Decarboxylation of β-Peroxy Lactones[1]

Summary: The lack of solvent effects on the activation parameters and product distribution and the lack of secondary deuterium isotope effects at the α carbon and β-alkyl migrant substantiate that the thermal decarboxylation of β-peroxy lactones proceeds via a 1,5-diradical.

Sir: On the basis of product distribution and kinetics[2] and stereochemical data[3] we concluded that the mechanism of thermal decarboxylation of β-peroxy lactones 1 involved simple peroxide bond cleavage leading to the 1,5-diradical 2, which subsequently decarboxylated with concurrent β-alkyl 1,2-migration to afford rearrangement ketone 3 as the major product (eq 1). Since evidence for 1,5-diradicals is scarce[4] and



1a, $R_1 = R_2 = R_3 = R_4 = CH_3$
b, $R_1 = R_2 = CH_3$; $R_3 = R_4 = CD_3$
c, $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = Ph$
d, $R_1 = R_2 = H$; $R_3 = CD_3$; $R_4 = Ph$
e, $R_1 = R_2 = D$; $R_3 = CH_3$; $R_4 = Ph$

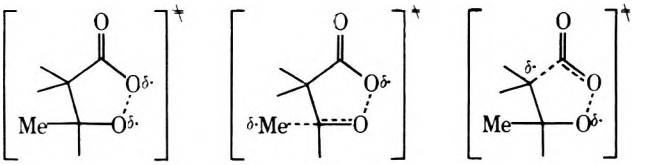


(1)

since the preferred alkyl vs. phenyl 1,2-shift is unusual,[2] it was of interest to confirm the diradical nature of this decarboxylation by exploring the effect of solvent polarity on the kinetics and product distribution in the β-peroxy lactone **1a** and the secondary deuterium isotope effect at the migration origin in β-peroxy lactones **1a** vs. **1b** and **1c** vs. **1d** and at the migration terminus in **1e** vs. **1c**.

The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of β-peroxy lactone **1a** for the solvents carbon tetrachloride, cyclohexane, benzene, and acetonitrile are summarized in Table I. Only a threefold rate enhancement has been observed between the least and most polar solvents, i.e., c-C_6H_{12} and CH_3CN. If the diradical-like activated complex A were sensitive to solvent polarity by possessing appreciable dipolar character, we would have to expect rate effects by several magnitudes.[5] Also the activation parameters are essentially constant within the experimental error, although a $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ plot is linear with an isokinetic temperature $T_{iso} = 583$ K. Whether the latter is mechanistically significant is debatable, but these solvent effect data reflect diradical character with only small dipolar contributions in polar solvents such as acetonitrile.

The isotope effect data is collected in Table I. In β-peroxy lactones **1a** vs. **1b** and **1c** vs. **1d** we were interested in probing whether the β-methyl group (the migrant) was cleaving from the β carbon concurrently with peroxide bond fission via the two-bond breaking activated complex B. Clearly, the negligible isotope effect reveals that neither in **1b** nor in **1d** has any significant methyl group scission taken place in the slow step, i.e., during peroxide bond cleavage.



A B C

In the case of β-peroxy lactones **1c** vs. **1e** we were interested in assessing the degree of α-carbon cleavage via the two-bond breaking activated complex C. Again, the negligible isotope effect signifies that peroxide bond rupture is not assisted by substantial α-carbon cleavage in the β-peroxy lactones not bearing α substituents. For example, an appreciable secondary isotope effect ($k_H/k_D = 1.17$) has been observed in *tert*-butyl phenylperacetate on deuteration of the benzylic position.[6] However, in this acyclic case a two-bond cleavage is encouraged, since the incipient benzyl radical is resonance stabilized.[7] In fact, in our cyclic case α substitution does lower the activation free energy by 3 kcal/mol, i.e., **1a** ($\Delta G^{\ddagger} = 28$ kcal/

Table I. Activation Parameters and Secondary Isotope Effects[a] in the Thermal Decarboxylation of β-Peroxy Lactones

β-Peroxy lactone	Solvent	T, K	$k_{avg} \times 10^3$, s^{-1} [b]	$\Delta H^{\ddagger}$,[c] kcal/mol	$\Delta S^{\ddagger}$,[c] gibbs/mol	$\Delta G^{\ddagger}_{383\ K}$,[d] kcal/mol	k_H/k_D
1a	CCl_4	383	0.627 ± 0.012	28.7 ± 0.3	1.7 ± 0.4	28.0 ± 0.4	
1a	c-C_6H_{12}	383	0.518 ± 0.010	28.6 ± 0.2	1.4 ± 0.3	28.1 ± 0.5	
1a	C_6H_6	383	0.916 ± 0.020	28.3 ± 0.4	1.0 ± 1.2	27.9 ± 0.5	
1a	CH_3CN	383	1.47 ± 0.05	26.7 ± 0.2	1.8 ± 0.6	27.4 ± 0.6	
1a	CCl_4	392	1.26 ± 0.04				
1b	CCl_4	392	1.26 ± 0.03				0.99 ± 0.03
1c	CCl_4	403	5.77 ± 0.03				
1d	CCl_4	403	5.70 ± 0.02				1.01 ± 0.03
1c	CCl_4	403	5.77 ± 0.03				
1e	CCl_4	403	5.85 ± 0.04				0.99 ± 0.03
1c	C_6H_6	398	5.92 ± 0.10[e]				
1d	C_6H_6	398	5.85 ± 0.15[e]				1.02 ± 0.02

[a] All deuterated substrates are at least 95% labeled, as confirmed by NMR and/or MS analysis. [b] Measured by disappearance of the 1790-cm^{-1} carbonyl band of **1** in the infrared except for the last two entries. The initial [**1**] was ~0.01 M. [c] From triplicate runs at 370, 383, and 391 K. [d] Calculated from $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. [e] These are methyl vs. phenyl migration ratios determined by quantitative GLC of the respective rearrangement ketone **3**. These ratios bear no units.

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mol) vs. **1c** ($\Delta G^{\ddagger}$ = 31 kcal/mol[2]), since a tertiary radical site is generated at the α carbon in the activated complex C.[8]

The β-peroxy lactones **1c** and **1d** were also employed to determine the secondary isotope effect during the 1,2-shift of the β-methyl migrant, i.e., in the destruction of the 1,5-diradical **2** into products. For this purpose, by means of quantitative GLC the migratory aptitudes of methyl (k_{Me}) vs. phenyl (k_{Ph}) as a function of methyl deuteration were measured by determining the amount of β-methyl vs. β-phenyl migration product. From β-peroxy lactones **1c** and **1d** the migratory ratios k_{CH_3}/k_{Ph} and k_{CD_3}/k_{Ph}, respectively, were obtained from which k_H/k_D was calculated. A negligible secondary isotope effect was found. This implies, as expected, that the slow step of the decomposition of β-peroxy lactones is the peroxide bond cleavage into diradical **2**. Subsequently, this diradical **2** decarboxylates with β-alkyl migration via a fast step with a low activation barrier. In such cases the secondary isotope effect is expected to be very small.[9] The error in our product data is too large to pick up such small effects.

The product distribution derived from **1a** was found to be insensitive to solvent polarity. Thus, pinacolone was formed essentially quantitatively (>99% yield) and only small amounts (<0.5%) of acetone and tetramethyloxirane (stable to the thermolysis conditions) could be detected in the various solvents. Consequently, also the destruction of the diradical **2** into pinacolone exhibits negligible dipolar character.

In conclusion, our present solvent and isotope effect data substantiate the previously proposed diradical mechanism (eq 1).[2,3] The intervention of the 1,5-diradical is established; however, we have no information on its lifetime. Experiments to trap **2** have failed so far, which implies that the 1,5-diradical must be shorter lived than 10^{-7} s. A carbonyl-^{18}O labeling experiment is in progress to estimate the lower lifetime limit of this 1,5-diradical.

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Superoxide in Organic Synthesis: A New Mild Method for the Oxidation of Amines to Carbonyls via *N*-Chloramines

Summary: Conversion of amines to their chloramines followed by reaction with potassium superoxide is a mild method of oxidizing amines to carbonyl compounds.

Sir: *N*-Chloramines have been used as effective intermediates for converting amines to their carbonyl derivatives in a number of synthetic schemes.[1,2] We wish to report here a new, mild method employing potassium superoxide and the results of our study on seven representative amines, including several unsymmetrical secondary amines.

We have converted a series of amines to their corresponding *N*-chloramines in ether solution utilizing the method of Bachmann[2] and without prior isolation reacted the chloramines with potassium superoxide (see Scheme I). In a typical experiment *N*-methylbutylamine (**1g**) (20 m.mol) in ether (50 mL) was converted to its chloramine. Additional ether (50 mL) was then added and the solution washed with water (1 × 50 mL), 1.5 M sulfuric acid (1 × 50 mL), and again with water (2 × 50 mL). It was then dried for at least 1 h over a mixture of magnesium sulfate, potassium carbonate, and molecular sieves.[3] After filtration the ether solution was slurried at room temperature with potassium superoxide (2.2 equiv) in the presence of 18-crown-6 polyether (80 mg). When the yellow superoxide color had completely faded (4–6 h), the mixture was filtered and the filtrate was poured into 2,4-dinitrophenylhydrazine reagent.[4] The ether was evaporated on a rotary evaporator and the crude 2,4-dinitrophenylhydrazone (2,4-DNP) of *n*-butyraldehyde was isolated (82% yield). Analysis of the product by TLC (silica, ether/petroleum ether, 20:80) showed only a minor trace of a material with an R_f similar to that of formaldehyde 2,4-DNP.[5] After recrystallization the melting point and mixed melting point confirmed the product to be *n*-butyraldehyde 2,4-DNP. See Table I for other examples.

The aldimines derived from diisobutylamine, di-*n*-pentylamine, and di-2-methylbutylamine have been isolated and their structures confirmed by IR (C=N stretch, 1670 cm^{-1}) and NMR (δ 7.6, 1 H, aldiminic). In the case of diisobutylamine pure *N*-chloramine was isolated and found to react in anhydrous ether to give imine[6] in 88% yield by analytical VPC, showing the reaction of KO_2 with *N*-chloramines is a clean, high-yield reaction.

An interesting result of our studies is our observation that elimination from unsymmetrical chloramines shows a preference for the more highly alkylated double bond, especially in the case of secondary methylamines. Thus *N*-chloro-*N*-methylbutylamine gives an overwhelming predominance of butylidenemethylamine on reaction with KO_2. Although imines have been shown to form from *N*-chloramines, very little work has been done with chloramines of secondary amines and we are unaware of any studies on product yields from unsymmetrical amines. We believe the high regioselectivity we have observed the mild conditions required, and the easy workup may have valuable synthetic applications in the removal of NCH_3 units from secondary methylamines.

Although the yield of carbonyl product from *n*-hexylamine was only moderate, no attempt was made to maximize the yield. Reaction of *N*-chlorohexylamine with KO_2 was more vigorous than with the secondary *N*-chloramines. Lowering the temperature of the reaction might enhance the yield.

Scheme I

$$R_2CHNHR' \xrightarrow{t\text{-BuOCl}} R_2\overset{Cl}{\overset{|}{C}}HNR' \xrightarrow{KO_2} R_2C{=}NR \xrightarrow{E^+} R_2C{=}O$$

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Table I. KO_2 Reaction with *N*-Chloramines

	Amine (1)	Product (3)	% yield
a	Diisobutylamine	$(CH_3)_2CHCH{=}NCH_2CH(CH_3)_2$	88[a]
b	Di-*n*-pentylamine	$CH_3(CH_2)_3CH{=}N(CH_2)_4CH_3$	73[b]
c	Di-2-methylbutylamine	$EtCHCH_3CH{=}NCH_2CHCH_3Et$	71[b]
d	Dibenzylamine	$PhCH{=}NCH_2Ph$	77[b]
e	*N*-Ethylcyclohexylamine	$C_6H_{10}{=}NCH_2CH_3$	40[b]
f		$C_6H_{11}N{=}CHCH_3$	23[b]
g	*N*-Methylbutylamine	$CH_3(CH_2)_2CH{=}NCH_3$	76[b]
h		$CH_3(CH_2)_3N{=}CH_2$	Trace[b]
i	*n*-Hexylamine	$CH_3(CH_2)_4CH{=}NH$	49[b]

[a] VPC yield of aldimine; see ref 6. [b] Isolated as 2,4-dinitrophenylhydrazone; see ref 7.

In an attempt to elucidate the mechanism we considered the possibility of a base-catalyzed reaction similar to Bachmann's.[2] However, KO_2 is no more basic than potassium acetate[8] and potassium acetate gave no imine when reacted under conditions used with KO_2. Using Na_2O_2 under these conditions, peroxide ion, a suspected product[9] of the reaction of KO_2 with *N*-chloramines, also gave no imine. When KOH was reacted with *N*-chloro-*N*-methylbutylamine, less than a 26% yield of imine was formed in the same time KO_2 gave an 82% yield. The KOH reaction was also considerably dirtier, giving several as yet unidentified products. We are therefore examining the reaction in detail for other possible intermediates.

Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, and the Old Dominion University Research Foundation for the support of this research.

References and Notes

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(2) W. E. Bachmann, M. P. Cava, and A. S. Drieding, *J. Am. Chem. Soc.*, **76**, 5554 (1954).
(3) Thorough drying of the ether solution is required because KO_2 decomposes in the presence of water.
(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 330.
(5) We estimate that the crude product is >95% pure.
(6) Satisfactory elemental analysis (within 0.3%) was obtained on this compound. The yield of **3a** is based on amount of *N*-chloramine used.
(7) The structures of compounds **3b–i** were confirmed by comparison of the melting points and mixed melting points of their 2,4-dinitrophenylhydrazones with those of authentic compounds. Yields are based on amount of starting amine used.
(8) The pK_a's of the conjugate acids of superoxide and acetate are the same (4.8): see D. Behar, G. Czapski, J. Rabani, L. M. Dorfman, and H. A. Schwarz, *J. Phys. Chem.*, **74**, 3209 (1970).
(9) The white solid material at the end of the reaction appears to be a 50:50 mixture of KCl and KOCH. Acidification gave within 10% the theoretical amount of oxygen to be expected from decomposition of KOOH.

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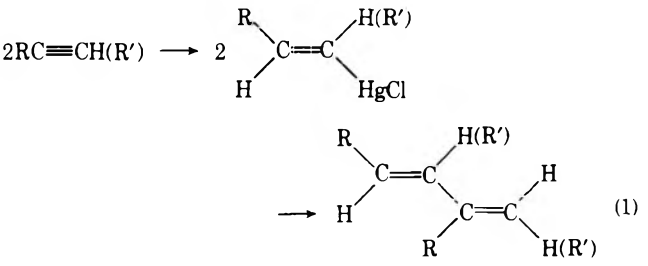
Mercury in Organic Chemistry. 15.[1] A Novel Stereospecific Synthesis of 1,3-Dienes via "Head-to-Tail" Dimerization of Alkynes

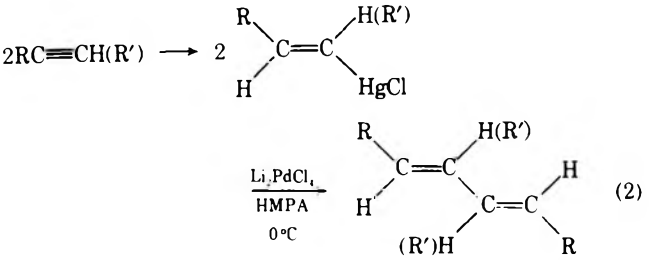
Summary: Terminal and internal alkynes can be dimerized in a "head-to-tail" fashion to provide excellent yields of unsymmetrical 1,3-dienes by preparing the corresponding vinylmercurial and treating it with palladium chloride and triethylamine in benzene at room temperature.

Sir: 1,3-Dienes have proven very valuable as intermediates in organic synthesis. Recently a number of interesting new organometallic methods have been reported for the stereospecific dimerization of terminal alkynes to 1,4-disubstituted 1,3-dienes.[2-9] For example, utilizing intermediate vinylboranes one can now prepare in a highly stereospecific manner cis,cis,[4] cis,trans,[5-7] or trans,trans[8,9] 1,4-disubstituted 1,3-dienes at will. We wish to report a novel new method employing vinylmercurials which produces unsymmetrical 1,3-dienes via "head-to-tail" dimerization of terminal and internal alkynes (eq 1).



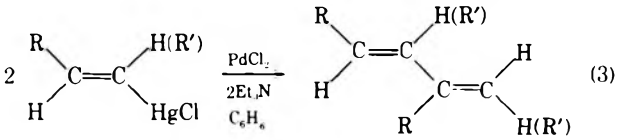
(1)

A while ago we reported a procedure for the symmetrical dimerization of vinylmercurials derived from both internal and terminal alkynes (eq 2).[10] Although the original procedure



(2)

required stoichiometric amounts of lithium chloride and palladium chloride in hexamethylphosphoramide (HMPA) at 0 °C in order to obtain high yields, we have more recently found that all of the disadvantages of that procedure can be overcome by using only catalytic amounts of $[ClRh(CO)_2]_2$ to effect the dimerization.[11] Upon closer examination of the palladium reactions we have observed that "head-to-tail" dimerization can occur in these same reactions simply by varying the reaction conditions. In fact, by omitting lithium chloride and employing less polar solvents, we are able to obtain the unsymmetrical 1,3-dienes in excellent yield. Best results are obtained by using 0.5 equiv of $PdCl_2$ and employing benzene as the solvent. It was also observed that HCl is generated during the course of these reactions and the addition of triethylamine improves the yields dramatically (eq 3).



(3)

The following procedure for the synthesis of *trans*-1,3-di-*n*-butyl-1,3-butadiene is representative. *trans*-1-Hexenylmercuric chloride (10 mmol) and palladium chloride (5

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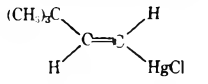
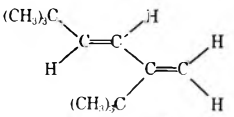
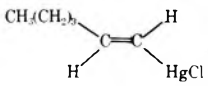
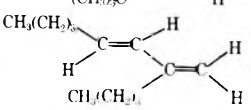
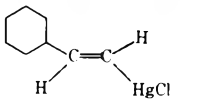
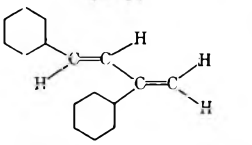
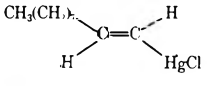
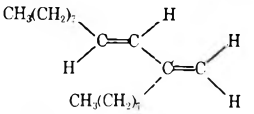
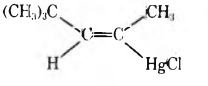
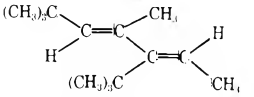
Table I. Synthesis of "Head-to-Tail" Dienes

Vinylmercurial	Diene	Time, h	Yield, %[a]
		24	91 (6)[b]
		12	98 (2)
			[93] (2)
		29	91 (2)
		24	[88] (5)
		16	62 (3)
			[59] (3)

[a] GLC yield using an internal standard; [isolated yield]; (yield of symmetrical 1,3-diene impurity). [b] No triethylamine used.

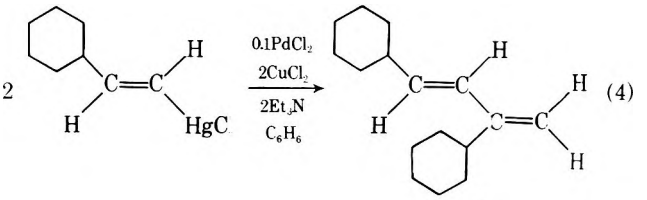
mmol) were placed in a round-bottom flask under nitrogen and 100 mL of benzene was added by syringe while cooling in an ice bath. Triethylamine (10 mmol) was quickly added and the ice bath removed. The reaction was then stirred for 12 h at room temperature. Charcoal and 5 mL of saturated ammonium chloride solution were added and stirred for 15 min. The mixture was filtered and the organic layer was separated, washed with dilute acid and base, and dried. Evaporation of benzene and column chromatography (pentane) on neutral aluminum oxide provided the 1,3-diene in 93% yield (98% pure by GLC analysis): bp 73–74 °C (7 mm); MS *m/e* 166.1721 ± 0.8 (calcd for $C_{10}H_{22}$, 166.1722); IR (max) (CCl_4) 3090 (=CH_2), 3030 (*trans*-CH=CH), 1650 (diene), 1610 (diene), 965 (*trans*-CH=CH), 885 (=CH_2) cm^{-1}; ^1H NMR (CCl_4) δ 0.92 (t, 6 H, J = 6 Hz, CH_3's), 1.4 (m, 3 H, CH_2's), 2.1 (m, 4 H, allyl), 4.78 (br s, 2 H, =CH_2), 5.3–6.1 (m, 2 H, -CH=CH-). The yields and isomeric purities of other 1,3-dienes are summarized in Table I. Yields determined by GLC analysis (DC-550 or SE-30 columns) were run on one-tenth the above scale using a hydrocarbon internal standard.

Only in the synthesis of *trans*-1,3-di-*tert*-butyl-1,3-butadiene was it found advantageous to omit the triethylamine. In this case the infrared spectral data is very similar to that above and the NMR spectral data clearly exhibits a trans coupling constant of J = 16 Hz. Spectral data and analyses for all other compounds are consistent with the assigned structures.

Since the reaction would achieve even greater synthetic utility were it to be effected using only catalytic amounts of palladium chloride, we have examined this possibility. Although the reaction is catalytic as run above, the catalyst turnover is generally quite low. However, addition of 2 equiv of anhydrous cupric chloride gives excellent yields using the exact procedure described above and only 10% palladium chloride (eq 4, 5).

We have also studied the analogous stoichiometric reactions of vinylalanes, -boranes, and -silanes, but only very low yields of unsymmetrical 1,3-dienes were obtained and these were contaminated by substantial amounts of the symmetrical 1,3-dienes.

The overall synthetic transformation is remarkable. The



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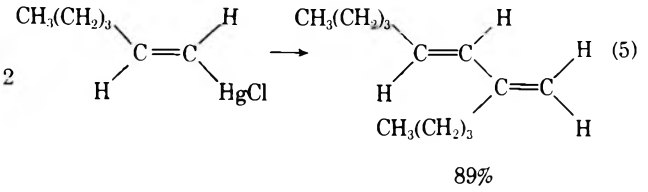
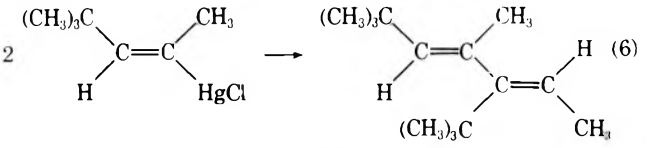


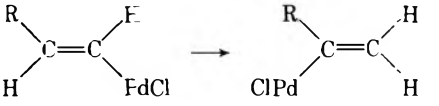
(5)

"head-to-tail" 1,3-dienes are obtained in excellent yields with only small amounts of the "head-to-head" and none of the "tail-to-tail" products. This is even true in the case of the vinylmercurial derived from 4,4-dimethyl-2-pentyne, where neither electronic nor steric effects would seem to favor formation of the "head-to-tail" diene and yet it is obtained in high purity and good yield (eq 6).



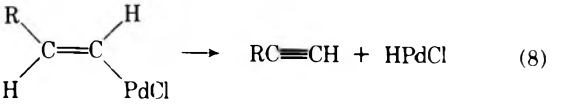
(6)

Although no totally satisfactory mechanism has yet been formulated, the reactions appear to involve palladium hydride rearrangement of an intermediate organopalladium compound (eq 7). The acid generated during the reaction quite



(7)

possibly arises from decomposition of an intermediate vinylpalladium species (eq 8, 9). However, questions remain



(8)

$$HPdCl \longrightarrow HCl + Pd \qquad (9)$$

as to the role of mercury in these reactions, the driving force for rearrangement, the reason for failure to observe statistical mixtures of all three possible 1,3-dienes, and just what species is involved in the coupling reaction.

During the course of our investigation an apparently related process for the "head-to-tail" dimerization of terminal alkynes was reported.[12] Although the combination triisobutylalane and bis(*N*-methylsalicylaldimine)nickel(II) directly dimerizes terminal alkynes, the yields are generally low and numerous side products are observed. It seems likely that this reaction involves nickel hydride promoted coupling in a manner analogous to our palladium reactions.

In conclusion, both terminal and internal alkynes can be dimerized in a "head-to-tail" fashion by preparing the corresponding vinylmercurial[13,14] and treating it with palladium chloride and triethylamine in benzene at room temperature. This reaction can also be effected using only catalytic amounts of palladium chloride if anhydrous cupric chloride is employed as a reoxidant. Excellent yields of 1,3-dienes are obtained using either procedure. The mechanism of this remarkable transformation, however, remains obscure.

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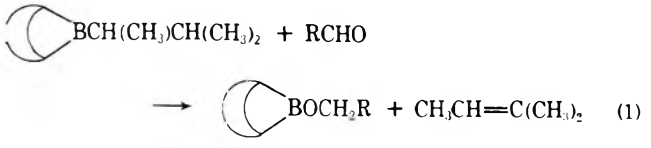
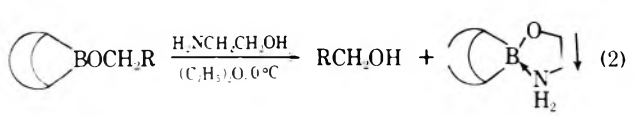
B-Alkyl-9-borabicyclo[3.3.1]nonanes as Mild, Chemoselective Reducing Agents for Aldehydes

Summary: *B*-Siamyl-9-BBN will reduce a variety of functionalized aldehydes to the corresponding alcohols even in the presence of unhindered ketones.

Sir: Certain *B*-alkyl-9-borabicyclo[3.3.1]nonanes (9-BBN) have been shown to be effective reducing agents for benzaldehyde. The efficiency of these compounds as reducing agents is largely dependent on the structure of the alkyl group on 9-BBN.[1] We wish to report that *B*-(3-methyl-2-butyl)-9-borabicyclo[3.3.1]nonane (*B*-siamyl-9-BBN)[2] is an effective reagent for the reduction of a wide variety of aldehydes under mild conditions.[3] The formation of an intermediate alkoxyborane is accompanied by the liberation of 2-methyl-2-butene (eq 1).[4] The boron species is conveniently removed by pre-



cipitation as the ethanolamine complex, leaving the alcohol in solution. Several representative examples of successful



conversions of aldehydes are presented in Table I, which illustrates a number of attractive features of the reagent system.

Table I. Reduction of Aldehydes to Alcohols with *B*-Siamyl-9-BBN

Product[a]	% yield[b]
$CH_3(CH_2)_4CH_2OH$	103 (54)
$(CH_3)_3CCH_2OH$	101 (49)
$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CHCH_2OH$[c]	100 (76)
$C_6H_5CH{=}CHCH_2OH$[d]	82 (62)
$C_6H_5CH_2OH$	97 (90)
p-$ClC_6H_4CH_2OH$	92 (80)
p-$CH_3OC_6H_4CH_2OH$	97 (65)
p-$(CH_3)_2NC_6H_4CH_2OH$	(92)
p-$O_2NC_6H_4CH_2OH$	(76)

[a] All compounds exhibited satisfactory spectra in accord with the assigned structure. [b] Determined by GLC using calibrated internal standard, numbers in parentheses indicate isolated yields. [c] A mixture of 61% geranial and 39% neral; the same ratio of geraniol and nerol was obtained. [d] *trans*-Cinnamaldehyde; the product had spectral properties identical with those of *trans*-cinnamyl alcohol.

First, trialkylboranes are exceedingly tolerant of many functional groups.[5] For example, *B*-siamyl-9-BBN reduces α,β-unsaturated aldehydes to allylic alcohols with neither detectable conjugate reduction nor 1,4 addition of the alkylborane in the absence of oxygen.[6] Branched or highly hindered aliphatic aldehydes are reduced almost as rapidly as straight-chain aldehydes; hexanal is reduced only slightly faster than pivaladehyde. The rate of reduction of para-substituted benzaldehydes is increased by electron-withdrawing groups and decreased by electron-donating groups. Benzaldehyde is reduced about ten times faster than *p*-dimethylaminobenzaldehyde.

Perhaps the most remarkable feature of the *B*-alkyl-9-BBN compounds is their ability to selectively reduce aldehydes in the presence of ketones. While a number of reagents[7] have been devised which show similar discrimination, only diisopropyl carbinol on alumina is reported to be sufficiently selective to reduce an aldehyde in preference to an unhindered cyclohexanone.[7g] We have found that substantial reduction of a wide variety of ketones is attained only after many days at reflux with *B*-siamyl-9-BBN.[8] Cyclohexanone itself is reduced only to the extent of 2–3% under conditions for aldehyde reduction. Indeed, a competition between benzaldehyde and acetophenone for a single equivalent of *B*-siamyl-9-BBN resulted in a >95% reduction of the aldehyde in 2 h with no detectable reduction of the ketone.[9]

Two substrates, *p*-dimethylaminobenzaldehyde and *p*-nitrobenzaldehyde, proved troublesome since the intermediate alkoxyborane could not be subjected to the usual workup conditions without incurring decomposition. Modified procedures for these allowed isolation of the alcohols with no further complications.

A general procedure for aldehyde reduction is as follows. A dry, 200-mL flask with a side arm covered by a rubber septum, containing a magnetic stirring bar, and surmounted by a reflux condensor connected to a mercury bubbler, was flushed with nitrogen. To the flask was added 62 mL of a 0.5 M solution of 9-BBN in THF (31 mmol), followed by 3.4 mL of distilled 2-methyl-2-butene (32 mmol). The mixture was stirred at reflux for 2 h. Then 30 mmol of freshly distilled aldehyde was injected into the flask.[10,11] Solid aldehydes were first dissolved in a small volume of THF and the solution was introduced into the reaction vessel via syringe. At the end of 2 h of reflux the solution was cooled to room temperature. Then ~0.2 mL of acetaldehyde was injected into the flask to destroy excess organoborane and the solution was stirred for 15 min. The solvent and volatile components were removed

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by water aspirator while stirring vigorously in a 40 °C water bath. The oily residue was dissolved in 30 mL of anhydrous diethyl ether and the solution was cooled in an ice bath. Then 1.85 mL of ethanolamine (31 mmol) was injected with rapid stirring. The precipitate was filtered on a fritted-glass funnel and washed with 5 mL of ether. The filtrate was washed with 60 mL of a saturated sodium chloride solution, dried ($MgSO_4$), and concentrated under vacuum to yield the crude product. The alcohol may be isolated by distillation at reduced pressure or by chromatography and is generally pure by NMR and GLC.

The capacity of *B*-alkyl-9-BBN compounds as chemoselective as well as enantioselective[12] reducing agents for aldehydes has been demonstrated.[13] The reagent is exceptionally mild since the reaction proceeds under essentially neutral conditions. The Meerwein–Pondorf–Verley type of mechanism proposed for this reduction[1] suggests that this reagent should possess unique properties. We are continuing to investigate both the mechanism and scope of these reactions.

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(8) Ketones may be reduced in a reasonable time if the concentration of the organoborane is increased.
(9) All ketones tested were reduced at least 100–200 times slower than the aldehydes. *B*-Siamyl-9-BBN is slightly more reactive toward acetophenone than toward cyclohexanone.
(10) When *p*-nitrobenzaldehyde was reduced, the reaction was conducted at room temperature for 3 h. After destroying excess organoborane with acetaldehyde, the solvent was removed under vacuum at room temperature. The residue was dissolved in 200 mL of ether and 1.85 mL of ethanolamine was added. The solution was filtered and the ether was concentrated under vacuum to about 3 mL (a drop or two of methanol will redissolve any precipitate). The product was eluted with ether from a silica gel column then concentrated by rotary evaporator and distilled by Kugelrohr at 0.01 mmHg, 110 °C. The alcohol was obtained as light yellow crystals in 76% yield, mp 67–69 °C.
(11) *p*-Dimethylaminobenzaldehyde was refluxed for 8 h. The solution was cooled to room temperature and treated with 2 mL of water, stirred for 15 min, then extracted with 2 × 30 mL of acidified water (concentrated HCl added dropwise until the solution had a pH of 1). The aqueous extracts were combined, made basic to pH paper (with 3 N sodium hydroxide solution), and extracted with 2 × 20 mL of ether (saturing the water with potassium carbonate after the first extraction). The combined extracts were dried over magnesium sulfate, filtered, and concentrated under vacuum to yield the product (pure by NMR).
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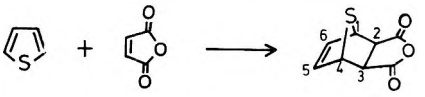
Diels–Alder Reaction of Thiophene with Maleic Anhydride at Very High Pressure[1,2]

Summary: The Diels–Alder reaction of thiophene with maleic anhydride proceeds under very high pressure conditions, affording the exo adduct.

Sir: There has been current interest in the Diels–Alder reaction of thiophenes. Because of the high aromaticity, it is a well-known fact that thiophene itself is inert to maleic anhydride.[3] The only recorded thiophene derivatives which are able to react with maleic anhydride in a Diels–Alder manner are thiophene 1,1-dioxide[4] and 2,5-dimethoxythiophene.[5] Recently it has been reported that some simple thiophene derivatives can combine with extremely reactive dienophiles such as dicyanoacetylene and dimethyl acetylenedicarboxylate.[6-10]

In this communication we wish to report the successful Diels–Alder reaction of thiophene with maleic anhydride at very high pressure (eq 1). In this way the 7-thiabicyclo[2.2.1]-hept-2-ene skeleton **3** is simply accessible.[11]



1 + **2** → **3** (1)

Thiophene failed to react with maleic anhydride in methylene chloride at 15 kbar and room temperature for 3 days. The reaction without solvent or with a Lewis acid catalyst (e.g., $MgCl_2$) was also fruitless.[12] These facts show a striking absence of diene character in thiophene, and contrast remarkably with the case of furan.[2] However, when we examined the reaction at higher temperatures at 15 kbar for 3 h in methylene chloride, we found that the reaction does occur (Table I). Inspection of the Table I reveals that the most favorable result is obtained at 100 °C. Thus, from the reaction mixture a highly crystalline compound **3**, mp 159.5–161.5 °C, of molecular formula $C_8H_6O_3S$ (MS, M^+ 182) was obtained in yields of 37–47% after recrystallization from ether or chloroform. On the stereochemistry of the adduct **3**, it is suggested that **3** has exo configuration from spectral data and chemical evidence as follows. In the ^1H NMR spectra, the C_2 and C_3 protons appear at δ 3.63 as a doublet signal (J = 1 Hz). When the dihedral angle between protons at C_1 and C_2 and also at C_3 and C_4 is taken into account, this fact indicates that **3** has exo configuration.[13] In agreement, the half methyl ester derived from **3** did not undergo iodolactonization (I_2–KI).[14]

Subsequently, the effect of solvent in the formation of the adduct **3** was investigated (Table II). The low yield in benzene is presumably due to the freezing of reaction medium at very high pressure.[15]

The following procedure for the Diels–Alder reaction of thiophene with maleic anhydride is representative.[16] A methylene chloride solution (1 mL) of thiophene (3 mmol) and

Table I. Temperature Dependence of the Yield [a] in the Adduct 3 between Thiophene and Maleic Anhydride

Room temp	No reaction	100 °C	37–47%
40 °C	No reaction	120 °C	18%
80 °C	8%	150 °C	Decomp

[a] The yield based on the isolated material.

Table II. Solvent Dependence of the Yield in the Adduct 3 between Thiophene and Maleic Anhydride (100 °C)

CH_2Cl_2	$CHCl_2CHCl_2$	C_6H_6	AcOEt
37–47%	47%	6–7%	15–19%

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maleic anhydride (3 mmol) was injected into the Teflon reaction vessel of ~0.85 mL capacity. The reaction vessel was heated to 100 °C at 15 kbar for 3 h. After cooling of the reaction mixture to room temperature and pressure release, the solvent was evaporated and the product was recrystallized from ether or chloroform to give pure **3** in yields of 37–47%: mass spectrum (20 eV) *m/e* (rel intensity) 132 (36, M^+), 110 (27), 84 (44), 78 (100), 66 (25), 45 (12); IR (Nujol) 1850, 1795, 1085, 943, 920 cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-d_6) δ 3.63 (d, J = 1 Hz), 4.59 (m), 6.61 (dd, J = 2, 3 Hz).

All attempted reactions between thiophene and other dienophiles such as dimethyl maleate, dimethyl fumarate, methyl acrylate, acrylonitrile, and acrolein under same conditions (100 °C, 15 kbar, 3 h, 3 M in methylene chloride) were fruitless, and no signs of adduct formation were observed.[17]

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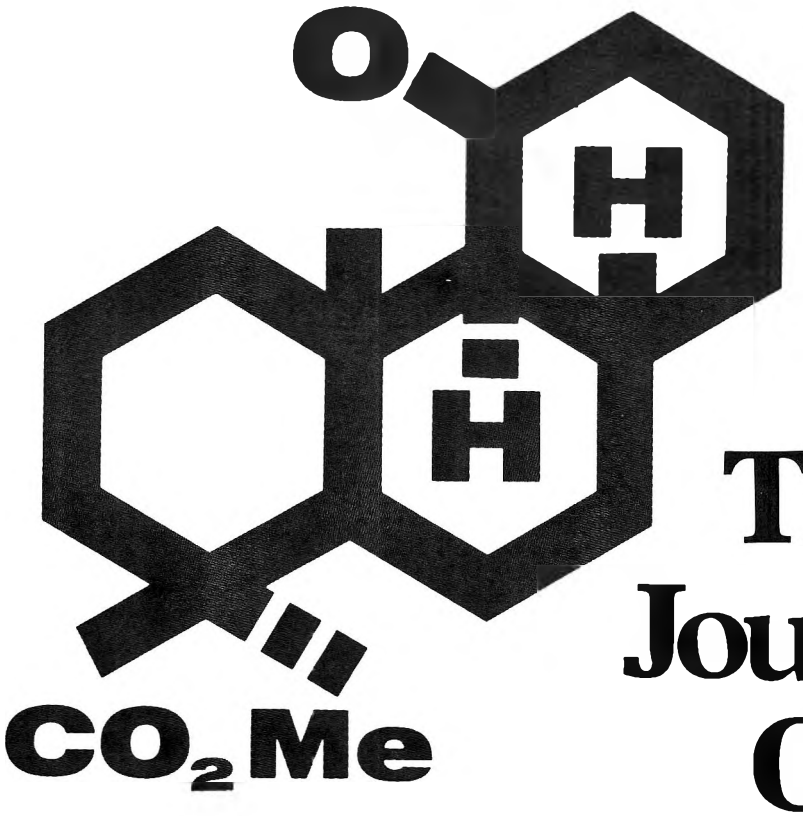

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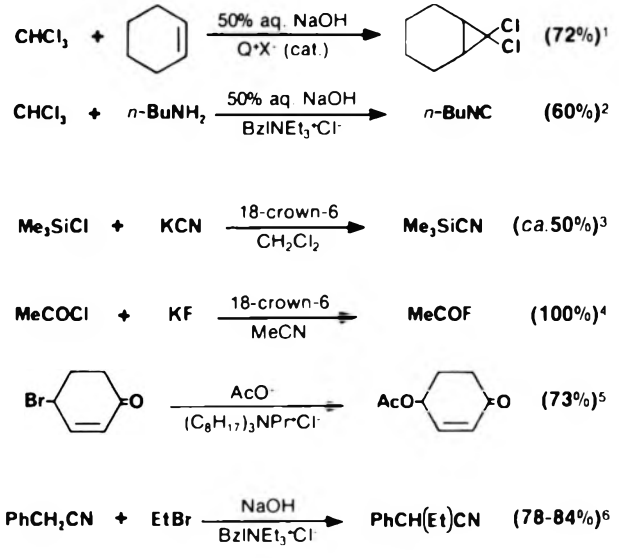

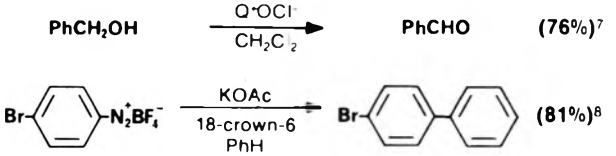

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