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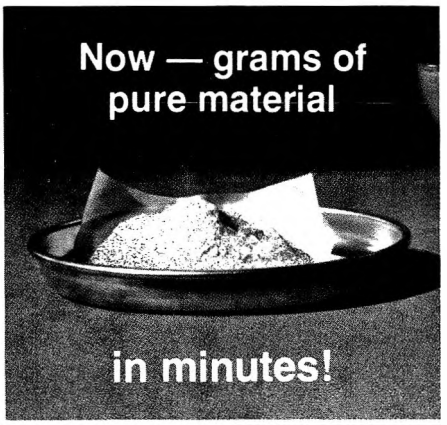

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A GRAVE SUBJECT

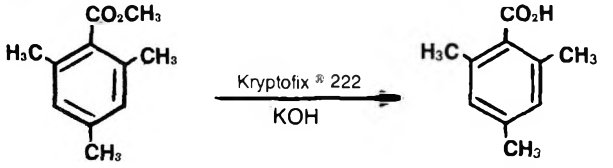
Imagine a chemical tomb; a repository or resting place for ions and small molecules; a sort of molecular vault. What a fascinating idea! In 1969 Dietrich, Lehn, and Sauvage at the Universite' Louis Pasteur in Strassbourg, France reported just such a class of compounds. These were the macrobicyclic diamine crown ether crypts I, II and IV.[1,2]

The crypts form stable complexes (cryptates) with alkali and alkaline earth cations[1-7] much like the planar crown ether complexes extensively investigated by Pedersen.[8] X-ray crystallographic studies indicate 1:1 stoichiometry with the metal ion positioned in the center of the ligand cavity and bound to nitrogen as well as the oxygen hetero atoms.[5-7] The rigid three dimensional crypts form much more stable complexes than the crowns as well as giving much greater selectivity between various cations. Table I lists stability constants of various cations with selected crypts[4] and crowns[9] in water at 25°.

TABLE I

Ligand	Log 10 Ks for Cations								
	Li	Na	K	Rb	Cs	Mg	Ca	Sr	Ba
Kryptofix® 222	< 2	3.0	5.3	4.3	< 2	< 2	4.4	8.0	9.5
Kryptofix® 221	2.5	5.3	3.9	2.5	< 2	< 2	6.9	7.3	6.3
Kryptofix® 211	4.3	2.8	< 2	< 2	< 2	-	2.8	< 2	< 2
18 crown 6		0.80	2.03	1.56	0.99	-	< 0.50	2.72	3.87
15 crown 5		0.70	0.74	0.62	0.8	-		1.95	1.71
Dicyclohexyl 18 crown 6									
cis syn cis	0.6	1.21	2.02	1.52	0.96				
cis anti cis		0.69	1.63	0.87	0.9				

The cryptates like the crown ether complexes have found synthetic utility as catalysts for promoting reactions which would otherwise be impractical or impossible. For example the hydrolysis of sterically hindered esters is greatly accelerated in the presence of the appropriate crypt or cryptate.

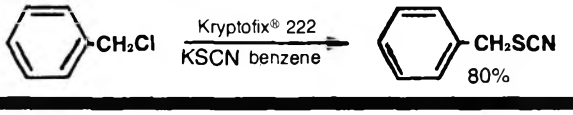


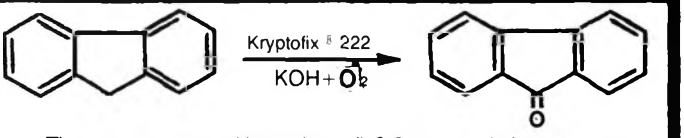
Data for the hydrolysis of methyl mesitoate are illustrated in table II.

TABLE II

Ligand	Solvent	Time	Temp.	Yield
none	1-propanol	5 hrs.	75°	0%
dicyclohexyl 18 crown 6	toulene	31 hrs.	74°	58%
Kryptofix® 222	toluene	12 hrs.	25°	80%
Kryptofix® 222	DMSO	2 min.	25°	50%

Although the crown ethers are also effective in catalyzing the reaction it is quite evident that the crypts allow higher yields with shorter reaction times and milder conditions. The reaction of benzyl chloride with potassium thiocyanate in the presence of 0.0001 mole of Kryptofix® 222 in chloroform for 6 days at room temperature gives an 80% yield of benzyl thiocyanate.





The same system without Kryptofix® 222 gives little or no reaction even after 10 days. Fluorene in the presence of potassium hydroxide and catalytic amounts of Kryptofix® 222 (0.0005 moles) in tetrahydrofuran is converted to the fluorenyl anion which may then be converted to fluorenone with oxygen.[10]

The remarkable selective complexing properties of the crypts render them suitable for a wide variety of interesting applications. The crypts are particularly useful in the concentration and separation of lead, silver, thallium, transition metals, actinides, uranium, and platinum.[10] The metals may be resurrected from the concentrated or purified crypt complex by treatment with a proton acid, lewis acid, quarternization of the amine or oxidation to the N-oxide with peracids. Other interesting applications are the selective decorporation of radioactive strontium, biological ion transport studies, and ion selective membrane electrodes. Interesting pharmacological activity has also been reported. For example N-alkylated Kryptofix® 22 compounds reportedly show antitiviral activity against A^2 influenza virus in the Hermann chick fibroblast tissue culture screen.[10] Kryptofix® 222 reportedly inhibits catechol amine induced free fatty acid mobilization which suggests utility in the treatment of diabetes and hyperlipemia.[10]

A host of interesting new developments almost certainly lies ahead. If you can't wait to get started on the next one drop us a line and we will forward a booklet containing additional information to help you along.

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10. J. M. Lehn U. S. Patent 3,888,877 June 10, 1975.

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■ Supplementary material for this paper is available separately (consult the masthead page for ordering information); it will also appear following the paper in the microfilm edition of this journal.

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AUTHOR INDEX

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JANUARY 21, 1977

The Chemistry of Carbanions. 30. Stereochemistry of the Metal–Ammonia Reduction of 7-*tert*-Butyl-10-methyl-$\Delta^{1,9}$-octal-2-one[1]

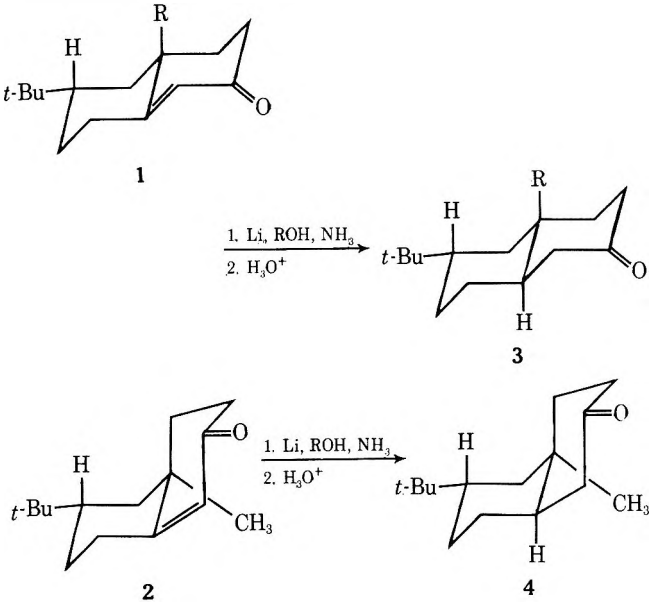
Herbert O. House* and Michael J. Lusch

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

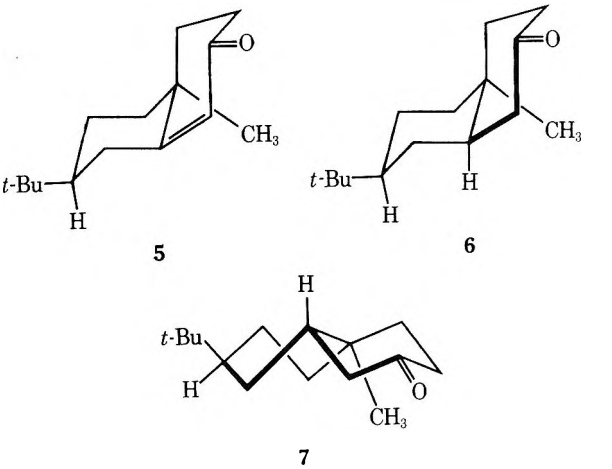
Received July 23, 1976

Several different routes, including reactions of several preformed metal enolates with methyl vinyl ketone, have been explored as synthetic routes to the octalone derivative **5**. This octalone **5** is held in an atypical conformation by a suitably placed *tert*-butyl substituent. As a result of this atypical conformation, reduction of the octalone **5** with Li in NH_3 produces mainly the cis-fused decalone derivative **6** (70% of the product) rather than a trans-fused decalone, the usual product of a metal–NH_3 reduction.

We are interested in exploring the use of a sterically bulky substituent to control the conformation of polycyclic systems and, as a result of this conformational control, to control the stereochemistry of reactions at sites remote from the location of the bulky substituent. This procedure for achieving stereochemical control would be an extension of the idea of conformational transmission.[2] An example of the use of this procedure to control reaction stereochemistry is provided by the reductions of enones **1** and **2** with Li and an alcohol in liquid NH_3. While reduction of the enone **1** (R = H[3] or CH_3[4]) produced the usual[5] trans-fused decalin derivative **3**, reduction of the epimer **2**[4,5] formed the atypical cis-fused decalin derivative **4**. Thus, the stereochemistry of this reduction is controlled by the location and stereochemistry of the remote *t*-Bu group.

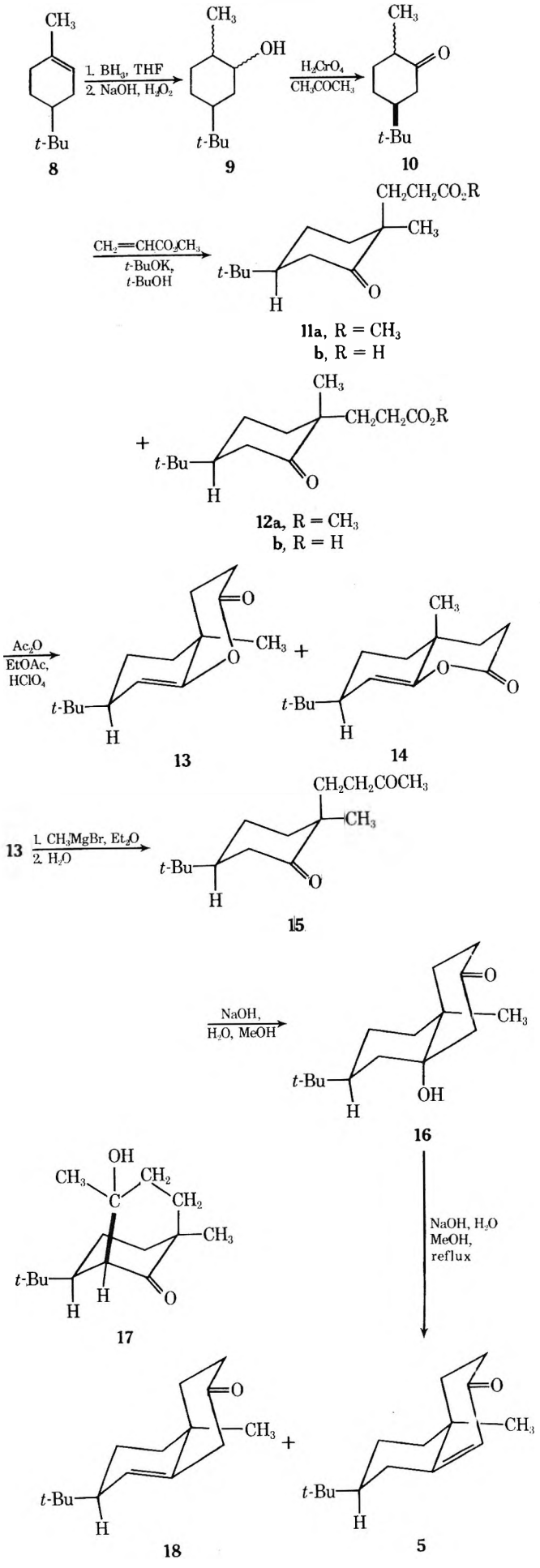


If this type of stereochemical control by a remote substituent is applicable to a number of reactions, it would clearly be profitable to find other substituents comparable to a *t*-Bu group in steric bulk (e.g., Me_3Si)[6] that could be introduced into a synthetic intermediate, used to control the stereochemistry of a reaction, and then removed. However, before exploring such groups that might be introduced temporarily to control conformation, it was clearly appropriate to examine other cases in which a remote *t*-Bu substituent might be effective in controlling reaction stereochemistry. This paper describes our study of another metal–NH_3 reduction, the conjugate reduction of the enone **5** to form either the cis or trans decalone derivatives **6** or **7**, and subsequent publications will describe stereochemical studies of other reactions.



In order to prepare a sample of the enone **5** of known stereochemistry we made use of a previously studied sequence[7] in which the olefin **8** (Scheme I) was converted successively to the alcohol **9**, the ketone **10**, and the two epimeric Michael adducts **11a** and **12a**. In the last step of this sequence,

Scheme I



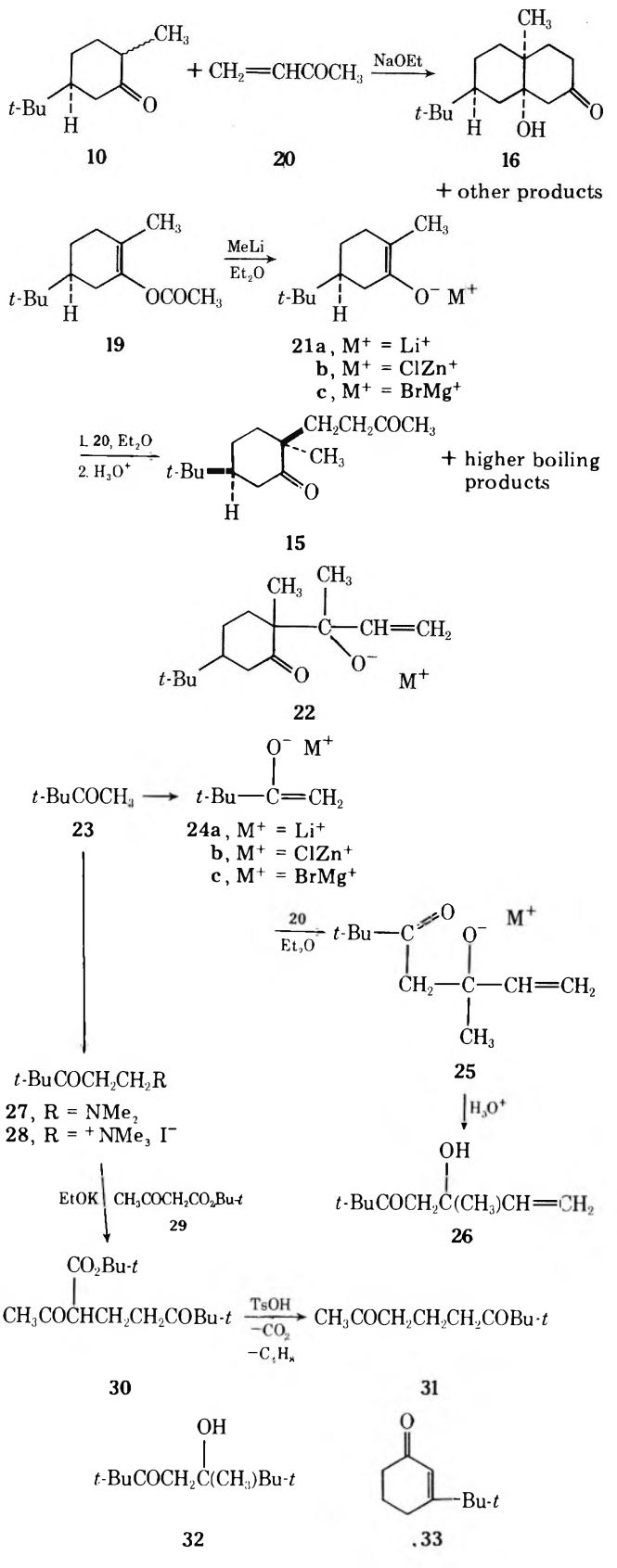
more than 85% of the Michael adduct was the epimer **11a** with an axial carbomethoxyethyl group.[7] Reaction of the corresponding mixture of keto acids **11b** and **12b** either with Ac_2O in EtOAc containing a catalytic amount of $HClO_4$[8] or with refluxing Ac_2O containing a catalytic amount of NaOAc[9] produced a mixture of epimeric enol lactones **13** and **14** from which the more abundant stereoisomer **13** was readily isolated by crystallization. Reaction of the enol lactone **13** with an equimolar amount of MeMgBr followed by hydrolysis[9,10] gave the diketone **15** with the desired stereochemistry. Reaction of this diketone with dilute NaOH at 25 °C yielded the corresponding ketol **16**; interestingly, we obtained no evidence indicating the formation of the isomeric ketol **17**. Reaction of the ketol **16** with excess NaOH in refluxing MeOH produced the desired enone **5** accompanied by 4–5% of its double bond isomer **18**.

In agreement with the stereochemical assignment given (Scheme I) for compound **16** in which the bridgehead Me group is axial to the cyclohexanone ring, the ^1H NMR signal for this Me group was shifted upfield 14 Hz when the solvent was changed from CCl_4 to C_6D_6.[11] By contrast, in the diketone **15** where the Me group is equatorial to the cyclohexanone ring, the NMR Me signal exhibited the expected[11] slight downfield shift (4.5 Hz) when the solvent was changed from CCl_4 to C_6D_6. Although conversion of the keto ester **11** of known stereochemistry via intermediates **13**, **15**, and **16** to the enone **5** served to establish the stereochemistry of this enone, it was clearly desirable to find a more direct synthetic route to the enone **5**. The fact that the desired ketol stereoisomer **16** was a relatively high-melting crystalline solid permitted us to obtain this ketol **16** in 24–31% yield by fractional crystallization of the product mixtures obtained from direct reaction of the ketone **10** and methyl vinyl ketone (**20**, Scheme II) in the presence of a catalytic amount of NaOEt.[12]

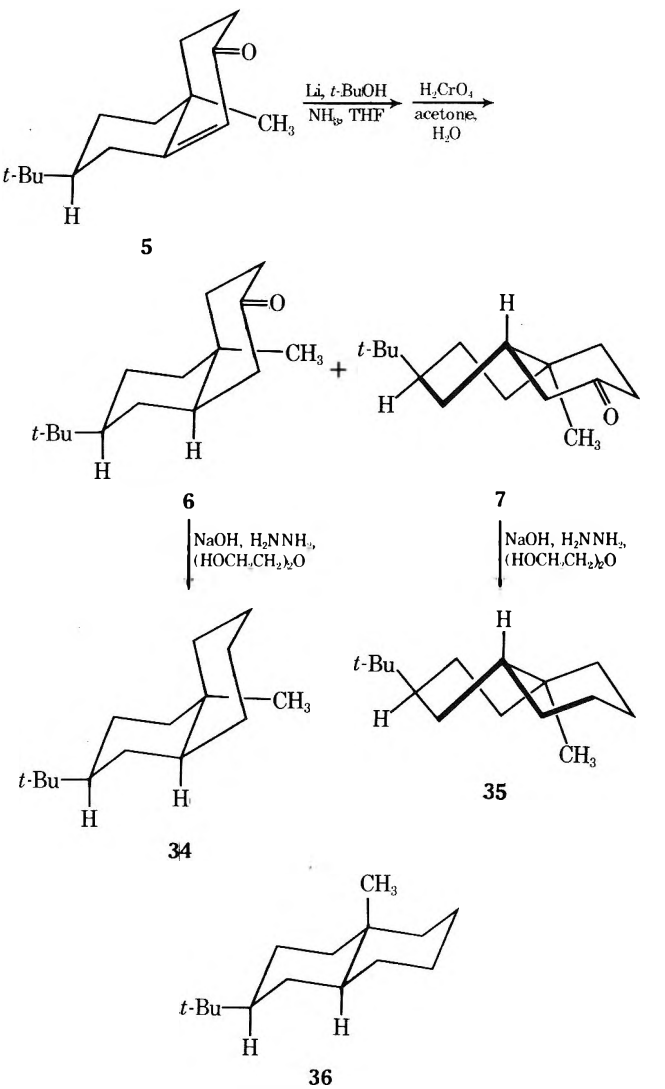
In an effort to improve the overall yield of the enone **5**, we also examined the reaction of methyl vinyl ketone **20** with the preformed metal enolates **21**. The Li enolate **21a** was obtained from the enol acetate **19**[13] and the ClZn (**21b**) and BrMg (**21c**) enolates were prepared by reaction of the Li enolate (**21a**) with $ZnCl_2$ or $MgBr_2$.[14] The best yields of the diketone **15** (54–55%) were obtained by reaction of either the Li enolate **21a** or the BrMg enolate **21c** with 1 equiv of methyl vinyl ketone (**20**) in Et_2O solution at −35 to −45 °C; the other products were the ketone **10** and higher molecular weight products from multiple condensation reactions. Thus, in this case the kinetically favored aldol product **22** evidently is sufficiently sterically congested that it dissociates to allow the slower (but energetically favored) formation of the Michael adduct (the enolate of **15**) to proceed. Although we observed similar results in reactions of the analogous metal enolates of 2-methylcyclohexanone with methyl vinyl ketone, the formation of Michael adducts from preformed metal enolates and methyl vinyl ketone is not a general reaction. In particular, with the less sterically congested metal enolates **24**, the same reaction conditions described above yield largely the kinetically favored aldol adduct **25**. This less sterically congested adduct **25** does not dissociate significantly under the reaction conditions described so that only very small amounts (<1%) of the Michael product **31** were formed. A similar reaction of the relatively unhindered Li enolate **24a** with cyclohexenone was previously observed to form only the aldol adduct.[15] Thus, the use of preformed metal enolates as precursors for Michael adducts from enones appears to be limited to situations in which the kinetic favored aldol adducts (e.g., **22**) have sufficient steric congestion to favor their dissociation.[16]

Although the foregoing studies demonstrated that a somewhat better yield of the diketone **15** could be obtained by employing a Michael reaction of the preformed BrMg enolate **21c** with methyl vinyl ketone (**20**), this benefit was offset

Scheme II



Scheme III



by the fact that three steps (**10** → **19** → **15** → **16**) were needed to convert the ketone **10** to the ketol **16**. Consequently, we utilized the NaOEt-catalyzed reaction of the ketone **10** with the enone **20** to obtain the bulk of the ketol **16** needed for preparing the enone **5**. Reduction of this enone **5** with the usual Li–NH_3–*t*-BuOH system produced a mixture containing mainly the cis-fused ketone **6** (70% of the product) accompanied by lesser amounts of the trans-fused ketone **7** (30% of the product, see Scheme III). To establish the stereochemistry of the ketone products **6** and **7**, the products were converted to the corresponding hydrocarbons **34** and **35** by Wolff–Kishner reduction. The product from the major ketone product **6** was shown to be identical with the previously characterized[17] cis-fused hydrocarbon **34**. The trans-fused hydrocarbon **35** was clearly different from the previously described[17] isomeric trans-fused decalin **36**.

Thus, the Li–NH_3 reduction of the enone **5** gives results similar to those indicated[4] for the reduction of the enone **2**. In both cases, the unusual conformation conferred upon the molecules by the bulky *tert*-butyl group in an appropriate stereochemical arrangement leads to the predominant formation of cis-fused decalone derivatives in spite of the very large preference for trans-fused decalones normally expected in a metal–NH_3 reduction.[5]

Experimental Section[18]

Preparation of the Keto Esters 11a and 12a. Reaction of 31.54 g (207 mmol) of the olefin **8** with 114 mmol of BH_3[19] in 146 ml of THF for 1 h at 3–25 °C followed by the addition of 10 ml of H_2O and oxidation with 25 ml of aqueous 3 M NaOH and 25 ml (250 mmol) of aqueous 30% H_2O_2 at 35–55 °C for 1 h yielded 38.66 g of the crude mixture of stereoisomeric alcohols **9**.[20] These alcohols **9** in 20 ml of H_2O and 100 ml of acetone were oxidized with 69.0 ml (1.33 equiv) of Jones reagent[21] for 45 min to yield, after fractional distillation, 25.11 g (72% based on the olefin **8**) of the ketone **10**, bp 88–90 °C (4.4 mm), n^{25}D 1.4570 [lit.[7] bp 99–105 °C (10 mm), n^{25}D 1.4562], containing (GLC, TCEP on Chromosorb P) the two stereoisomers of ketone **10** [retention times 7.5 (major) and 8.0 min (minor)] as well as a small amount of 4-*tert*-butylcyclohexanone (9.2 min). To a solution of *t*-

BuOK, from 237 mg (6.05 mg-atoms) of K, and 9.255 g (55.0 mmol) of the ketone **10** in 50 ml of *t*-BuOH was added 5.208 g (60.5 mmol) of methyl acrylate, dropwise during 5 min with stirring and cooling (mixture kept at 25–30 °C). After the mixture had been stirred for an additional 5 min, it was neutralized with aqueous 2 M HOAc and subjected to the usual isolation procedure to separate 11.29 g (81%) of the product as a colorless liquid, bp 106–112 °C (0.23 mm) [lit.[7] bp 92–99 °C (0.2 mm)], containing (GLC, LAC-728 on Chromosorb P) the known[7] keto esters **11a** (ca. 88%, retention time 13.8 min) and **12a** (ca. 12%, 21.7 min).

Preparation of the Enol Lactone 13. A mixture of 5.087 g (20.0 mmol) of the keto esters **11a** and **12a** and 60 ml of aqueous 20% HCl was refluxed with stirring for 18 h and then cooled and extracted with Et_2O. An Et_2O solution of the acidic product (from extraction with $NaHCO_3$) was dried and concentrated to leave 4.536 g (93.8%) of a mixture of keto acids **11b** and **12b** as a white solid: mp 88–93.5 °C; IR (CCl_4), 1710 cm^{-1} (carboxyl C=O); UV max (95% EtOH) 290 nm (ϵ 34.5); NMR (CCl_4) δ 11.57 (1 H, s, OH), 1.2–2.7 (11 H, m, aliphatic CH), 0.90 (9 H, s, *t*-Bu), and two singlets (total 3 H) at 1.14 (minor, axial CH_3 of **12b**) and 0.97 (major, equatorial CH_3 of **11b**). Although this product recrystallized easily from hexane, the recrystallized product (mp 88.5–104 °C) contained (NMR analysis) the same mixture of isomers **11b** and **12b** present in the initial product.

After a solution of 51.07 g (0.50 mol) of Ac_2O, 0.05 ml (0.6 mmol) of aqueous 70% $HClO_4$, and 5.153 g (21.4 mmol) of the mixture of keto acids **11b** (major) and **12b** (minor) in 500 ml of EtOAc[8] had been stirred at 25 °C for 15 min, it was partitioned between EtOAc and aqueous $NaHCO_3$ and the organic layer was separated, dried, and concentrated. The residue was treated with MeOH and pyridine to remove the residual Ac_2O and again concentrated. A solution of the residual yellow liquid (4.828 g, a mixture of lactones **13** and **14**) in pentane when cooled to 0 °C deposited 2.805 g (59%) of the pure (GLC) enol lactone **13** as white plates: mp 52.5–53.5 °C; IR (CCl_4) 1764 (enol ester C=O) and 1679 cm^{-1} (enol C=C); UV (95% EtOH) end absorption with ϵ 5440 at 210 nm; NMR (CCl_4) δ 5.30 (1 H, d, J = 2.5 Hz, vinyl CH), 2.4–2.7 (2 H, m, CH_2CO), 1.3–2.2 (7 H, m, aliphatic CH), 1.13 (3 H, s, CH_3), and 0.88 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 222 (M^+, <1), 207 (1), 166 (24), 165 (100), 137 (50), 109 (29), 55 (36), and 41 (17); calcd for $C_{14}H_{22}O_2$, 222.1620; found, 222.1605. When the NMR spectrum was measured in C_6D_6, the CH_3 singlet was shifted upfield 14 Hz (to 53 Hz) relative to its position (67 Hz) in CCl_4 solution. This upfield shift is consistent with the CH_3 group being axial to the lactone ring.[11]

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.61; H, 9.97.

The lactone **13** was very sensitive to air oxidation and was best stored under an N_2 atmosphere in a refrigerator. In an alternative preparation, a solution of 3.382 g (14.1 mmol) of the mixture of keto acids **11b** and **12b** and 30 mg of NaOAc in 25 ml of Ac_2O was refluxed[9] for 5 h and then subjected to the usual isolation procedure to yield 2.824 g of pale yellow liquid, bp 111–120 °C (0.05 mm), that solidified on standing. This crude product contained (GLC, Carbowax 20M on Chromosorb P) the lactones **13** (ca. 90%, retention time 43.3 min) and **14** (ca. 10%, 48.1 min). The NMR spectrum (CCl_4) of this product differed from the spectrum of the pure lactone in exhibiting two vinyl CH doublets at δ 5.30 (major, attributable to **13**) and 5.22 (minor, attributable to **14**). The NMR CH_3 signal for the minor enol lactone isomer **14** was not resolved from the *t*-Bu signal. In C_6D_6 solution, the NMR CH_3 signals for the lactones were found at δ 0.95 (lactone **13**) and 0.92 (lactone **14**). When a 2.561-g portion of this lactone mixture was recrystallized from pentane at 0 °C, 1.451 g of the pure lactone **13** was obtained, mp 52.5–53.5 °C.

Preparation of the Diketone 15 and the Ketol 16. A. From the Lactone 13. A cold (0 to −2 °C) solution of 454 mg (2.04 mmol) of the enol lactone **13** in 25 ml of Et_2O was treated with 1.5 ml of an Et_2O solution containing 2.04 mmol of MeMgBr,[9,10] stirred at 0 to −3 °C for 3 h, and then partitioned between Et_2O and aqueous NH_4Cl. The Et_2O layer was washed with aqueous NaCl, dried, and concentrated to leave 491 mg of a pale yellow liquid that contained (IR and NMR analysis, GLC, Carbowax 20M on Chromosorb P) primarily the diketone **15** (retention time 40.8 min) accompanied by several minor unidentified components (6.0, 7.6, 14.0, 17.0, and 48.2 min). A collected (GLC) sample of the pure diketone **15** was obtained as a colorless liquid: $n^{25}D$ 1.4756; IR (CCl_4), 1719 and 1703 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 238 (M^+, <1), 168 (13), 95 (22), 69 (16), 57 (30), 55 (23), 43 (100), and 41 (48); NMR (CCl_4) δ 2.0–2.5 (7 H, m, CH_2CO and a $COCH_3$ singlet at 2.08), 1.2–2.0 (7 H, m, aliphatic CH), and 0.90 (12 H, s, CH_3 and *t*-Bu). In C_6D_6 solution, the NMR CH_3 singlets were found at δ 1.67 (CH_3CO), 0.98 (CH_3), and 0.70 (t-Bu). The shift, $\delta_{CCl_4} - \delta_{C_6D_6}$, for the CH_3 singlet is −4.5 Hz, consistent with the methyl group being equatorial[11] in the diketone **15**.

Anal. Calcd for $C_{15}H_{26}O$: C, 75.58; H, 11.00. Found: C, 75.66; H, 11.01.

A solution of 504 mg of the crude diketone **15** [from 454 mg (2.04 mmol) of the lactone **13**] and 1.041 g (26 mmol) of NaOH in 60 ml of MeOH and 10 ml of H_2O was stirred at 25 °C under an N_2 atmosphere for 24 h. The resulting yellow solution was concentrated and the residual slurry was partitioned between Et_2O and H_2O. After the Et_2O solution had been washed with aqueous NaCl and dried, concentration left 404 mg of the crude product as a pale yellow solid, mp 90–125 °C. Recrystallization from hexane separated 173 mg (35.6% based on the lactone **13**) of ketol **16** as white plates, mp 145–147 °C. Recrystallization gave the pure ketol **16**: mp 146.5–147.5 °C; IR (CCl_4) 3598, 3440 (OH), and 1719 cm^{-1} (C=O); UV (95% EtOH) maximum at 281.5 nm (ϵ 21) with end absorption, ϵ 385 at 210 nm; mass spectrum *m/e* (rel intensity) 238 (M^+, 2), 181 (16), 168 (100), 111 (28), 69 (36), 57 (77), 55 (58), 43 (84), and 41 (94); NMR ($CDCl_3$) δ1.1–3.0 [17 H, m, aliphatic CH including a CH_3 singlet at 1.21 and an OH singlet (exchanged with D_2O) at 1.62] and 0.83 (9 H, s, *t*-Bu). In C_6D_6 solution, the NMR CH_3 singlets were at δ 0.97 (CH_3) and 0.75 (*t*-Bu). The absence of a third CH_3 singlet in these NMR spectra indicates that the ketol has the structure **16** rather than the alternative structure **17**.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.64; H, 11.01.

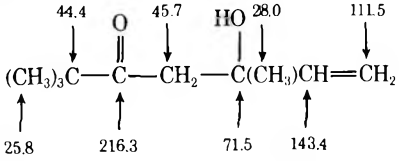
B. From the Ketone 10. A 0.25-ml (0.75 mmol) sample of a NaOEt slurry [from 1.724 g (75 mg-atoms) of Na with 25 ml of EtOH] was added to 1.683 g (10.0 mmol) of the cold (10 °C) ketone **10** and then 0.734 g (10.5 mmol) of $MeCOCH{=}CH_2$ was added, dropwise with stirring and cooling. Since the analysis of the crude reaction mixture indicated that unchanged ketone **10** remained, an additional 0.25 ml (0.75 mmol) of NaOEt slurry was added followed by the dropwise addition of a second equivalent (0.734 g or 10.5 mmol) of $MeCOCH{=}CH_2$. The resulting mixture was allowed to stand at −15 °C for 3 days and then partitioned between Et_2O and aqueous NH_4Cl. The Et_2O solution was washed with aqueous NaCl, dried, and concentrated to leave 3.20 g of crude product as a viscous orange liquid. Fractional crystallization from an Et_2O–hexane mixture separated 515 mg of the crude ketol **16**, mp 141–147 °C. The residue from the mother liquors was extracted with boiling hexane and the extract was decolorized with charcoal, concentrated, and chromatographed on silica gel with PhH as eluent to separate an additional 400 mg of the crude ketol **16** (total yield 0.91 g or 38%). Recrystallization from hexane separated 748 mg (31%) of the pure ketol **16** as white plates, mp 146.5–148.5 °C, identified with the previously described sample by a mixture melting point determination and comparison of IR spectra. In several additional experiments employing two 7.5–10 mol % portions of NaOEt with temperatures in the range −20 to −10 °C, the isolated yields of the recrystallized ketol **16** ranged from 24 to 30%. When two 1.9 mol % portions of NaOEt were employed, as recommended[12] for the preparation of the ketol from 2-methylcyclohexanone, the yield of ketol **16** was only 4%.

C. From the Metal Enolates 21. Previously described procedures were used to prepare a 0.73 M solution of anhydrous $ZnCl_2$ in Et_2O[14] and the enol acetate **19**, bp 63–65 °C (0.07 mm), $n^{25}D$ 1.4620–1.4626 [lit.[7] bp 70–76 °C (0.1 mm), $n^{25}D$ 1.4629]. Reaction of 169.1 (0.90 mol) of $BrCH_2CH_2Br$ with 24.3 g (1.00 g-atom) of triply sublimed Mg in 450 ml of Et_2O afforded a two-phase mixture of $MgBr_2$ and Et_2O from which some $(Et_2O)_2MgBr_2$ crystallized on standing. This mixture was diluted with 50 ml of PhH and 100 ml of Et_2O and the resulting solution was cooled on dry ice to deposit white, crystalline $(Et_2O)_2$-$MgBr_2$. This solid was recrystallized from a PhH–Et_2O mixture (1:2 v/v) and then redissolved in 250 ml of anhydrous Et_2O to again give a mixture of two liquid phases. The lower, more abundant phase was filtered through a Celite pad and then aliquots of the colorless to pale yellow solution were quenched in H_2O and titrated for Mg and Br. The concentration of $MgBr_2$ in the more dense liquid phase was 2.45 M.

A solution of the Li enolate **21a** was prepared[13,14] from 1.016 g (4.83 mmol) of the enol acetate **19** and 10.62 mmol of halide-free MeLi in 30 ml of Et_2O containing 387 mg of n-$C_{16}H_{34}$ (an internal standard) and then divided into three 10-ml aliquots, each containing 1.6 mmol of the enolate **21a**. One aliquot was treated with 3.6 mmol of $ZnCl_2$ in 5.0 ml of Et_2O and the resulting pale yellow suspension was stirred at 5 °C for 45 min. A second aliquot of solution was treated with 3.62 mmol of $MgBr_2$ in 1.5 ml of Et_2O and stirred at 0 °C for 30 min. Each of the three solutions, containing 1.6 mmol of one of the enolates **21**, was cooled to −40 to −45 °C and a solution of 121 mg (1.73 mmol) of $CH_3COCH{=}CH_2$ in 11.5 ml of Et_2O was added dropwise with stirring and cooling during 10 min. After the resulting mixtures had been stirred at −35 to −45 °C for 15 min, a 5-ml aliquot of the reaction

solution was withdrawn and quenched in a cold MeOH-Et_2O mixture. A second equivalent (1.73 mmol) of $CH_3COCH{=}CH_2$ in 11.5 ml of Et_2O was added to the remaining cold (−40 °C) reaction solutions. After the resulting solutions had been stirred at −35 to −40 °C for 5 min, a second aliquot was removed and quenched in cold MeOH-Et_2O. Each of the six reaction mixture aliquots from the above experiments was acidified with HOAc, and partitioned between Et_2O and aqueous NH_4Cl. The organic layers were washed successively with aqueous $NaHCO_3$ and aqueous NaCl, dried, concentrated, and analyzed by GLC (silicone SE-52 on Chromosorb W, apparatus calibrated with known mixtures). The GLC retention times for the various products follow: ketone **10**, 3.9 min; *n*-$C_{16}H_{34}$, 17.5 min; and diketone **15**, 32.2 min. Collected (GLC) samples of the diketone **15** from the reaction mixtures were identified with the previously described authentic sample by comparison of GLC retention times and NMR and IR spectra. The yields of diketone **15** from the various enolates **21** and 1 and 2 equiv of the enone **20** follow: **21a**, 54 and 7%; **21b**, 9 and 6%; **21c**, 55 and 45%. In a similar experiment where the lithium enolate **21a** was generated in THF solution and the cold (−40 to −45 °C) solution was treated with 1.1 equiv of MeCOCH=CH, the yield of diketone **15** was 42%.

Preparation of the Ketol 26. Following previously described procedures, a solution of the enolate **24a** was prepared[13,14] by adding a solution of 8.44 g (84 mmol) of the ketone **23** in 22 ml of Et_2O to a cold (−35 to −40 °C) solution of *i*-Pr_2NLi, from 11.19 g (111 mmol) of *i*-Pr_2NH in 80 ml of cold (−35 to −40 °C) Et_2O and 61 ml of a hexane solution containing 110 mmol of *n*-BuLi, and several milligrams of 2,2′-bipyridyl (an indicator). The resulting solution of enolate **24a** was warmed to −10 °C and treated with 76 ml of an Et_2O solution containing 55 mmol of anhydrous $ZnCl_2$. After the resulting pale orange solution of the enolate **24b** had been stirred at −10 to 0 °C for 15 min, it was divided into two equal aliquots each containing 42 mmol of the enolate **24b**. One portion of this enolate solution was kept at 3–5 °C while 5.525 g (78.8 mmol) of the enone **20** was added, dropwise and with stirring during 10 min. The resulting mixture, from which a white, granular precipitate separated, was stirred at 3–5 °C for 5 min and then partitioned between Et_2O and cold aqueous 1 M HCl. After the ethereal phase had been washed successively with aqueous $NaHCO_3$ and with aqueous NaCl, it was dried and concentrated to leave 7.78 g of a pale yellow liquid product that contained (IR and NMR analyses) the ketol **26**. Distillation in a short-path still separated 5.019 g (70.2%) of the pure ketol **26** as a colorless liquid: bp 48–58.5 °C (1.6 mm); $n^{25}D$ 1.4391–1.4400; IR (CCl_4), 3480 (associated OH), 1694 (C=O with intramolecular H bonding), 1643 (weak, C=C), and 930 cm^{-1} (*CH*=*CH*$_2$); UV max (95% EtOH) 288.5 nm (ε 41); NMR (CCl_4) δ 5.86 (1 H, d of d, *J* = 10.3 and 17.5 Hz, vinyl CH), two overlapping doublets of doublets at 5.14 (1 H, *J* = 17.5 and 2.0 Hz, vinyl CH) and 4.92 (1 H, *J* = 10.3 and 2.0 Hz, vinyl CH), 4.20 (1 H, broad s, OH, exchanged with D_2O), an AB pattern with *J* = 17.5 Hz at 2.83 and 2.49 (2 H, $COCH_2$), 1.21 (3 H, s, CH_3), and 1.07 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 170 (M^+, <1), 100 (20), 70 (21), 57 (100), 55 (54), 43 (74), 41 (53), and 39 (16). The natural abundance ^{13}C NMR spectrum ($CDCl_3$ solution) of the product is summarized in the following formula.

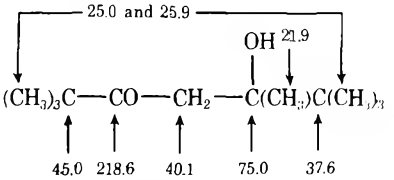


Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.55; H, 10.68.

The second aliquot of the solution containing 42 mmol of the enolate **24b** was maintained at −60 °C while 78.8 mmol of the enone **20** was added, dropwise and with stirring during 20 min. After following the previously described isolation procedure, distillation of the crude product separated 4.36 g (65.2%) of the ketol **26**, bp 50–57 °C (1.6 mm), $n^{25}D$ 1.4386–1.4392. In a comparable experiment, the reaction mixture obtained from the enone **20** and an Et_2O solution of the enolate **24b** was stirred for 2 h at 24–25 °C with periodic removal of aliquots for hydrolysis and NMR and IR analysis. No appreciable change in the nature of the crude product was evident during the prolonged reaction period. When a sample of the granular white precipitate present in the reaction mixture was separated and hydrolyzed, analysis (IR and NMR) again indicated the presence of the crude ketol **26**. A portion of the supernatant liquid from the reaction mixture appeared to contain (IR and NMR) mainly the ketone **23** after hydrolysis.

To learn whether a significant amount of the Michael adduct **31** could be obtained from reaction of one of the metal enolates **24** with the enone **20**, a cold (−35 to −40 °C) solution of the Li enolate **24a** was prepared using 3.97 g (39.2 mmol) of *i*-Pr_2NH, 7.2 ml of THF, 19.9 ml of Et_2O, 24.9 ml of a hexane solution containing 37.8 mmol of *n*-BuLi, and 3.627 g (36.2 mmol) of ketone **23** in 10 of Et_2O containing 604 mg of *n*-$C_{17}H_{36}$ (an internal standard). This solution was divided into three 24-ml aliquots, each containing 12 mmol of the enolate **24a**. One aliquot was mixed (at −5 to 0 °C) with 8.7 ml of an Et_2O solution containing 6.3 mmol of anhydrous $ZnCl_2$, stirred at 0 °C for 15 min. A second aliquot of the enolate solution was treated with 8.7 ml of Et_2O containing 12.7 mmol of anhydrous $MgBr_2$, and the resulting solution (containing some suspended solid) was stirred at −5 to 0 °C for 15 min. Each of the three enolate solutions was cooled to −50 to −60 °C, treated with 18.5 mmol of the enone **20**, stirred at −55 to −60 °C for 5 min, and then siphoned into cold aqueous 1 M HCl. From each of these reactions, the combined organic layer and ethereal extract of the aqueous phase were washed with aqueous $NaHCO_3$, concentrated, and subjected to GLC analysis (ethylene glycol adipate on Chromosorb P) employing apparatus calibrated with known mixtures of *n*-$C_{17}H_{36}$ (retention time 12.3 min) and the diketone **31** (18.8 min). When the ketol **26** was injected on this GLC apparatus, it dissociated to the rapidly eluted ketones **23** and **20**, and consequently did not interfere with the analysis for the diketone **31**. In the three reaction mixtures (each containing mainly the ketol **26**, NMR analysis), the calculated yields of diketone **31** were 0.08% from enolate **24a**, 0.47% from enolate **24b**, and 0.57% from enolate **24c**.

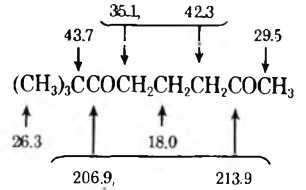
Preparation of the Ketol 32. A pale yellow solution of the enolate **24a**, from 5.49 g (54.3 mmol) of the ketone **23** and 54.3 mmol of *i*-Pr_2NLi in 90 ml of Et_2O and 30 ml of hexane, was maintained at −1 to 1 °C for 30 min while a solution of 5.49 g (54.3 mmol) of the ketone **23** in 15 ml of Et_2O was added, dropwise and with stirring. The resulting pale yellow solution was partitioned between Et_2O and cold aqueous 1 M HCl and the organic phase was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The residual pale yellow liquid (10.7 g) containing (IR and NMR analysis) the crude ketol was fractionally distilled to separate 8.66 g (79.6%) of fractions containing the pure ketol **32** as a colorless liquid: bp 60–67.5 °C (1.6 mm); $n^{25}D$ 1.4374–1.4390 [lit. bp 64–65 °C (0.9 mm),[22a] 89–90 °C (5 mm),[22b] 77 °C (3 mm);[22c] $n^{25}D$ 1.4378,[22a] 1.4384,[22b] 1.4390[22c]]; IR (CCl_4), 3488 (associated OH), and 1694 cm^{-1} (C=O with H bonding); UV max (95% EtOH) 290 nm (ε 44); NMR (CCl_4) δ 4.14 (1 H, s, OH, exchanged with D_2O), an AB pattern (*J* = 17 Hz) with signals at 2.82 and 2.37 (2 H, CH_2CO), 1.09 singlet with a partially resolved second signal at ca. 1.08 (total 12 H, *t*-Bu and CH_3), 0.89 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 185 (1), 143 (7), 100 (15), 85 (15), 57 (100), 43 (26), and 41 (33). The natural abundance ^{13}C NMR spectrum ($CDCl_3$ solution) of the product is summarized in the following formula.



Preparation of the Diketone 31. After a solution of 50.08 g (0.50 mol) of the ketone **23**, 17.57 g (0.585 mol) of paraformaldehyde, 47.7 g (0.585 mol) of Me_2NH_2Cl, and 0.8 ml of aqueous 12 M HCl in 65 ml of EtOH had been refluxed for 6 h, the solution was cooled to deposit 39.32 g (41%) of the hydrochloride of the amino ketone **27** as white plates. This material was partitioned between Et_2O and excess aqueous Na_2CO_3 and the organic phase was washed with aqueous NaCl, dried, and concentrated to leave 28.78 g (37%) of the crude amino ketone **27** as a pale yellow liquid: IR (CCl_4) 1703 cm^{-1} (C=O); NMR (CCl_4) δ 2.3–2.7 (4 H, m, CH_2), 2.14 (6 H, s, CH_3N), and 1.08 (9 H, s, *t*-Bu). A solution of this amine **27** (28.78 g, 183 mmol) in 100 ml of Et_2O was treated, portionwise and with stirring, with 32.5 g (229 mmol) of CH_3I. The white precipitate that separated was collected, washed with Et_2O, and dried to leave 48.66 g (89%) of the crude salt **28**, mp 184–188 °C dec. Recrystallization from absolute EtOH afforded 45.68 g (84%) of the methiodide **28** as fine, colorless crystals: mp 188–190 °C dec (lit.[23] mp 196 °C); IR (KBr pellet), 1703 cm^{-1} (C=O); NMR (D_2O) δ 3.15 (9 H, s, CH_3N), 2.8–3.1 (4 H, m, CH_2), and 1.17 (9 H, s, *t*-Bu).

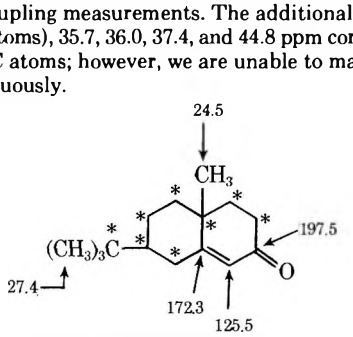
To a cold (0–2 °C) mixture of 16.46 g (55 mmol) of the methiodide **28**, 7.91 g (50 mmol) of the keto ester **29**, and 55 ml of PhH was added, dropwise and with stirring during 25 min, a solution of KOEt[24] prepared from 2.05 g (53 mg-atoms) of K and 29.3 ml of EtOH. After the resulting pale yellow to colorless suspension had been stirred at 0–2 °C for 3 h, it was filtered and the filtrate was concentrated under re-

duced pressure. The residual yellow semisolid was partitioned between H_2O and Et_2O and the organic phase was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl, and then dried and concentrated. The residual crude diketo ester **30** amounted to 13.5 g of pale yellow liquid: IR (CCl_4), 1739 (ester C=O) and 1714 cm^{-1} (C=O); NMR (CCl_4) δ 3.1–3.5 (1 H, m, CHCO), 1.7–2.7 (7 H, m, aliphatic CH including a CH_3CO singlet at 2.15), 1.43 (9 H, s, *t*-BuO), and 1.08 (9 H, s, *t*-Bu). A mixture of 6.76 g (25 mmol) of the crude diketo ester **30** and 48 mg (2.5 mmol) of *p*-TsOH was heated to 120–140 °C with stirring for 1 h at which time the gas evolution had subsided. The residual yellow liquid was distilled to separate 2.84 g (67%) of the diketone **31** as colorless to pale yellow fractions, bp 98–102 °C (5.5 mm), $n^{25}D$ 1.4365–1.4370. These fractions contained (GLC, ethylene glycol adipate on Chromosorb P) mainly the diketone **31** (retention time 15.5 min) accompanied by ca. 4% of an impurity believed to be the enone **33** (18.3 mm). A sample containing (GLC) mainly this impurity **33** was obtained by GLC collection: IR (CCl_4) 1671 (conjugated C=O) and 1614 cm^{-1} (conjugated C=C).[25] To separate the pure diketone **31**, a portion of the product containing ca. 96% of the diketone **31** was crystallized from hexane at ca. −25 °C and the resulting white needles (mp ca. −10 °C) were collected, allowed to melt, and rapidly distilled in a short-path still at 1.4 mm. The pure diketone **31** was obtained as a colorless liquid; $n^{25}D$ 1.4358; IR (CCl_4) 1713 and 1701 cm^{-1} (C=O); UV max (95% EtOH) 282 nm (ϵ 49); NMR (CCl_4) δ 2.2–2.7 (4 H, M, CH_2CO), 2.05 (3 H, s, CH_3CO), 1.5–2.0 (2 H, m, CH_2), and 1.08 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 170 (M^+, 1), 155 (2), 113 (100), 85 (75), 58 (30), 57 (82), 55 (24), 43 (93), and 41 (34). The natural abundance ^{13}C NMR spectrum ($CDCl_3$) of the diketone 31 is summarized in the following formula.



Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.54; H, 10.68.

Preparation of the Enone 5. A solution of 29.76 g (744 mmol) of NaOH, 300 ml of H_2O, and 17.74 g (74.4 mmol) of the ketol **16** (mp 146.5–147.5 °C) in 1800 ml of MeOH was refluxed for 18 h and then diluted with 500 ml of aqueous NaCl, concentrated, and extracted with Et_2O. The ethereal extract was washed with aqueous NaCl, dried, and concentrated to leave 16.13 g (98%) of the crude product as a yellow liquid that contained (IR analysis) practically pure enone **5**. This product exhibited one major GLC peak (silicone SE-52 on Chromosorb W) corresponding to the conjugated enone **5** (retention time 25.2 min) accompanied by a small amount (ca. 4%) of the β,γ isomer **18** (13.7 min). Distillation afforded 14.70 g (89.7%) of the enone **5** as a pale yellow liquid, bp 93–105 °C (0.03 mm). Redistillation gave the pure enone **5** as a very pale yellow liquid; bp 106–110 °C (0.03 mm); $n^{25}D$ 1.5130 [lit.[26] bp 85 °C (0.1 mm)]; IR (CCl_4) 1670 (conjugated C=O) and 1626 cm^{-1} (conjugated C=C); UV max (95% EtOH) 244 nm (ϵ 14 900) and 314.5 (74) [lit.[26] 242 nm (ϵ 12 600)]; ^1H NMR (CCl_4) δ 5.66 (1 H, broad, vinyl CH), 1.3–2.6 (11, H, m, aliphatic CH), 1.22 (3 H, s, CH_3), and 0.84 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 220 (M^+, 9), 164 (14), 149 (17), 121 (19), 91 (23), 79 (23), 77 (18), 57 (100), 55 (39), 43 (23), 41 (88), and 39 (31). The ^{13}C NMR spectrum of the enone **5** ($CDCl_3$ solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements. The additional peaks at 21.3, 31.7, 33.9 (2 C atoms), 35.7, 36.0, 37.4, and 44.8 ppm correspond to the designated (*)C atoms; however, we are unable to make the assignments unambiguously.



Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.81; H, 11.17.

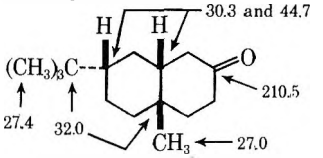
The enone **5** formed a 2,4-dinitrophenylhydrazone that crystallized from MeOH as crimson needles: mp 172–173.5 °C [lit.[26] mp 166–167.5 °C); IR ($CHCl_3$) 1619 (C=N, C=C), 1508, and 1339 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 11.2 (1 H, broad, NH), 9.13 (1 H, d, J = 2.5 Hz, aryl CH), 8.32 (1 H, d of d, J = 2.5 and 9.5 Hz, aryl CH), 7.97 (1 H, d, J = 9.5 Hz, aryl CH), 6.13 (1 H, broad, vinyl CH), 1.2–2.8 (11 H, m, aliphatic CH), 1.17 (3 H, s, CH_3), and 0.88 (9 H, s, *t*-Bu).

The crude enone 5 (558 mg containing ca. 4% of the β,γ isomer **18**) from another preparation was subjected to preparative low-pressure liquid chromatography employing a column packed with silica gel and eluted with Et_2O–hexane (1:9 v/v). The more rapidly eluted fractions contained a few milligrams of the crude β,γ isomer **18** that was distilled in a short-path still to separate the β,γ isomer **18** as a pale yellow liquid that solidified when cooled below 30 °C: IR (CCl_4) 1721 (C=O) and 1658 cm^{-1} (weak, C=C); NMR (CCl_4) δ 5.42 (1 H, broad, vinyl CH), 1.3–3.3 (11 H, m, aliphatic CH), 1.23 (3 H, s, CH_3), and 0.85 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 220 (M^+, 7), 164 (100), 163 (23), 149 (40), 107 (27), 91 (27), 79 (22), 57 (99), 55 (45), 41 (64), and 39 (21); calcd for $C_{15}H_{24}O$, 220.1827; found, 220.1826.

The latter fractions from this chromatograph contained 549 mg of the enone **5** as a pale yellow liquid identified with the previously described material by comparison of IR spectra.

Reduction of the Enone 5. To a cold (−33 °C) solution of 586 mg (84.4 mg-atoms) of Li in 150 ml of liquid NH_3 was added, dropwise and with stirring, a solution of 4.658 g (21.1 mmol) of the enone **5** and 3.144 g (42.4 mmol) of *t*-BuOH in 30 ml of THF. After the resulting mixture had been stirred under reflux for 20 min, solid NH_4Cl was added to consume the excess Li and the NH_3 was allowed to evaporate. The residue was partitioned between H_2O and Et_2O and the Et_2O solution was washed with aqueous NaCl, dried, and concentrated. The crude roduct, a yellow liquid containing (IR analysis) mainly the ketones **6** and **7** accompanied by some alcohol by-products, was dissolved in 100 ml of cold (0 °C) acetone, treated with a slight excess of aqueous 8 N H_2CrO_4,[24] and then treated with *i*-PrOH, diluted with H_2O, concentrated under reduced pressure, and again partitioned between H_2O and Et_2O. After the Et_2O solution had been washed successively with aqueous $NaHCO_3$ and with aqueous NaCl, it was dried and concentrated to leave 4.639 g (99%) of the crude product as an orange liquid. Distillation at 0.02 mm in a short-path still afforded 4.22 g (90%) of the mixture of ketones **6** and **7** as a pale yellow liquid. This mixture contained (GLC, silicone XE-60 on Chromosorb P) ca. 70% of the ketone **6** (retention time 21.8 min) and ca. 30% of the ketone **7** (25.9 min).

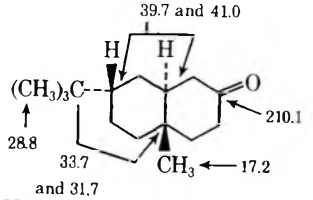
A collected (GLC) sample of the major isomer, ketone **6**, was obtained as a colorless liquid that solidified on standing, mp 48.5–50.5 °C. Recrystallization from pentane at dry ice temperature afforded the pure ketone: mp 50.8–51.8 °C; IR (CCl_4) 1712 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 1.0–2.9 (17 H, m, aliphatic CH including a CH_3 singlet at 1.22) and 0.84 (9 H, s, *t*-Bu); in C_6D_6 solution the ^1H NMR singlets were at δ 0.91 (CH_3) and 0.75 (*t*-Bu); mass spectrum *m/e* (rel intensity) 222 (M^+, 27), 167 (21), 166 (48), 109 (22), 108 (28), 96 (100), 95 (30), 81 (22), 57 (79), 55 (32), and 41 (43). The natural abundance ^{13}C NMR spectrum of the ketone **6** ($CDCl_3$ solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.



(signals for CH_2 groups at 22.2, 30.4, 37.5, 39.8, 44.5, and 48.2 ppm)

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.10; H, 11.95.

A collected (GLC) sample of the minor isomer, ketone **7**, was distilled in a short-path still at 0.02 mm to obtain the pure ketone as a colorless liquid: $n^{25}D$ 1.4893; IR (CCl_4) 1714 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 1.2–2.5 (14 H, m, aliphatic CH), 1.08 (3 H, s, CH_3), and 0.89 (9 H, s, *t*-Bu); in C_6D_6 solution the ^1H NMR singlets were at δ 0.74 (CH_3) and 0.79 (*t*-Bu); mass spectrum *m/e* (rel intensity) 222 (M^+, 13), 167 (35), 166 (49), 109 (20), 96 (24), 95 (29), 57 (100), 55 (24), and 41 (34). The natural abundance ^{13}C NMR spectrum of the ketone **7** ($CDCl_3$ solution) is summarized in the following formula; the indi-



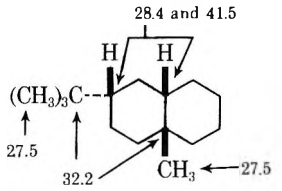
(signals for CH_2 groups at 21.2, 29.2, 37.8, 38.2, 41.4, and 44.9 ppm)

cated assignments are consistent with off-resonance decoupling measurements.

Anal. Cacld for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.31; H, 11.97.

To obtain quantitative data concerning the yields and product distributions of the ketones **6** and **7** from reduction of enone **5**, a series of small-scale reductions were performed in which the crude neutral product was mixed with an internal standard (n-$C_{19}H_{40}$) and subjected to GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The retention times for the various components follow: n-$C_{19}H_{40}$, 9.2 min; β,γ enone **18**, 19.0 min; ketone **6**, 22.4 min; ketone **7**, 27.0 min; α,β enone **5**, 46.2 min. In a typical reduction, a solution of 881 mg (4.0 mmol) of the enone **5** and 593 mg (8.0 mmol) of t-BuOH in 5.0 ml of THF was added to a solution of 111 mg (16.0 mg-atoms) of Li in 25 ml of liquid NH_3. After the resulting mixture had been stirred under reflux for 30 min, it was subjected to the previously described isolation procedure including treatment with aqueous H_2CrO_4 in acetone. The crude liquid product was mixed with a known weight of n-$C_{19}H_{40}$ and subjected to GLC analysis. In three independent runs the total yield of ketones **6** and **7** were 91, 97, and 98% and the average composition of the product was 70.0 ± 0.5% of ketone **6** and 30.0 ± 0.7% of ketone **7**.

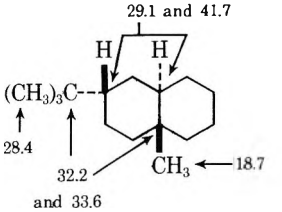
Preparation of the Hydrocarbon 34. A mixture of 607 mg (2.73 mmol) of the ketone **6**, 804 mg (13.7 mmol) of aqueous 85% H_2NNH_2, and 6.0 ml of $(HOCH_2CH_2)_2O$ was refluxed (N_2 atmosphere) for 1.25 h and then cooled and treated with 328 mg (8.19 mmol) of NaOH. The mixture was again heated to boiling, the H_2O and H_2NNH_2 were allowed to distill from the mixture, and the resulting solution was refluxed (N_2 atmosphere) for 3 h. The reaction mixture was partitioned between pentane and aqueous 10% HCl and the organic layer was washed with aqueous NaCl, dried, and concentrated to leave 527 mg (93%) of the crude hydrocarbon **34** (IR and GLC analysis, silicone DC-710 on Chromosorb P). Distillation separated 426 mg (75%) of the hydrocarbon **34** as a colorless liquid, bp 72.5–74 °C (0.14 mm), n^{25}D 1.4798–1.4801 (lit.[20] n^{25}D 1.4792), that was identified with an authentic sample by comparison of IR, NMR, and mass spectra and GLC retention times. The natural abundance ^{13}C NMR spectrum of the hydrocarbon ($CDCl_3$ solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.



(signals for CH_2 groups at 20.6, 22.2, 22.8, 28.1, 29.9, 42.1, and 48.7 ppm)

Preparation of the Hydrocarbon 35. The same reduction procedure was followed with 308 mg (1.38 mmol) of the ketone **7**, 406 mg (6.9 mmol) of aqueous 85% H_2NNH_2, 3.0 ml of $(HOCH_2CH_2)_2O$, and 166 mg (4.14 mmol) of NaOH. The crude neutral product, 260 mg (90%) of pale yellow liquid containing (IR and GLC analysis) the hydrocarbon **35**, was distilled in a short-path still at 1.5 mm to separate 222 mg (77%) of the pure hydrocarbon **35** as a colorless liquid: n^{25}D 1.4792; IR (CCl_4) no OH or C=O absorption; ^1H NMR (CCl_4) δ 1.0–2.0 (16 H, m, aliphatic CH), 0.86 (9 H, s, t-Bu), and 0.85 (3 H, s, CH_3); mass spectrum m/e (rel intensity) 208 (M^+, 2), 152 (52), 137 (31), 109 (39), 96 (45), 95 (100), 83 (32), 81 (49), 67 (32), 57 (73), 55 (43), and 41 (52).

The IR, NMR, and mass spectra of this hydrocarbon **35** were clearly different from the corresponding spectra of the known[17] hydrocarbons, **34** and **36**. The natural abundance ^{13}C NMR spectrum of the hydrocarbon **35** ($CDCl_3$ solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.



(signals for CH_2 groups at 21.2, 22.2, 26.9, 29.0, 39.3, 39.4, and 42.7 ppm)

Anal. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.44; H, 13.50.

After a number of GLC columns were examined, one GLC column (silicone OV-17 on Chromosorb P) was found that would partially resolve the cis hydrocarbon **34** (retention time 22.5 min) from the trans hydrocarbon **35** (23.2 min). On this same column, the previously described[17] trans hydrocarbon **36** had a retention time between those of hydrocarbons **34** and **35** so that a mixture of all three hydrocarbons exhibited a single broad GLC peak.

Registry No.—**5**, 13547-64-3; **5** DNPH, 60676-13-3; **6**, 60676-14-4; **7**, 60676-15-5; **8**, 3419-74-7; **9**, 15822-55-6; *cis*-**10**, 5951-22-4; *trans*-**10**, 5937-40-6; **11a**, 37818-70-5; **11b**, 60676-16-6; **12a**, 37786-90-6; **12b**, 60676-17-7; **13**, 60676-18-8; **15**, 60676-19-9; **16**, 60676-20-2; **18**, 60676-21-3; **19**, 37786-83-7; **20**, 79-94-4; **21a**, 37786-85-9; **21b**, 60676-22-4; **21c**, 60676-23-5; **23**, 75-97-8; **24a**, 34865-75-3; **24b**, 60676-24-6; **25**, 60676-25-7; **27**, 22700-73-8; **28**, 60676-26-8; **29**, 1694-31-1; **30**, 60676-27-9; **31**, 60676-28-0; **32**, 3205-30-9; **33**, 17299-35-3; **34**, 35096-26-5; **35**, 60676-29-1; methyl acrylate, 96-33-3; MeLi, 917-54-4; $ZnCl_2$, 7646-85-7; $MgBr_2$, 7789-48-2; i-Pr_2NLi, 4111-54-0.

References and Notes

(1) This research has been supported by Public Health Service Grant 9-RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

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(18) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV specta were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(19) A THF solution of BH_3 was standardized by the procedure described in the Aldrich Chemical Co. bulletin, "Quantitative Analysis of Active Boron Hydrides".

(20) We found this procedure, in which the crude alcohol **9** is separated, to be more satisfactory than the previously described (ref 7) procedure in which the organoborane was oxidized directly with aqueous H_2CrO_4.

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Stereochemistry of Organophosphorus Cyclic Compounds. 6.[1] Stereochemistry of the Reaction between Sulfenyl Chlorides and Trivalent Phosphorus Compounds[2]

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cis- and *trans*-2-methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (**3**) have been synthesized and their conformations studied by ^1H and ^{31}P NMR. *trans*-**3** is found to exist as a chair-form conformer with the ring methyl and phosphoryl group equatorial. *cis*-**3** adopts most likely a chair conformation with the ring methyl equatorial and phosphoryl group axial. It has been demonstrated that *cis*- and *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinanes (**1**) and 2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (**2**) react with a variety of sulfenyl chlorides stereospecifically with retention at phosphorus. The same steric course has been observed for reaction between optically active *O*-isopropyl ethylphosphinate (**12**) and *O*-isopropyl *O*-trimethylsilyl ethylphosphonite (**15**) and methylsulfenyl chloride. The mechanism of reaction of trivalent phosphorus compounds with sulfenyl chlorides is discussed.

The reaction between alkyl- and arylsulfenyl chlorides and trialkyl phosphites, which takes place to give the corresponding thiophosphates and alkyl chlorides according to eq 1, was first studied by Morrison[3] in 1955.

$$(RO)_3P + R'SCl \longrightarrow (RO)_2P(=O)-SR' + RCl \qquad (1)$$

Dialkyl phosphites react analogously although in this case thiophosphate formation is accompanied by the elimination of hydrogen chloride in place of the alkyl chloride.

Reaction 1 is usually regarded as an Arbuzov-type process involving decomposition of an intermediate phosphonium chloride.[4] However, neither the mechanism nor the steric course of this reaction has been investigated in detail.[5] We were prompted to undertake a detailed study of the mechanism of reaction 1 by consideration of the fact that the phosphite molecule can attack either the sulfur or the halogen atom of the sulfenyl halide molecule. Formally, this corresponds to the two possible modes of sulfur–chlorine bond polarization.

$$R-\overset{\delta^+}{S}(Cl^{\delta^-}) \overset{1}{\leftarrow} \overset{\cdot\cdot}{P}(OR)_3 \overset{2}{\rightarrow} \overset{\delta^+}{Cl}-\overset{\delta^-}{SR} \qquad (2)$$

One possible ionic mechanism consists in the nucleophilic attack of phosphite on sulfur leading to the formation of an intermediate "quasi-phosphonium salt" A (eq 3). Subsequent

$$(RO)_3P: + \overset{\delta^+}{R}S-\overset{\delta^-}{Cl} \longrightarrow \underset{A}{\left[(RO)_2\overset{+}{P}(O-R)-SR'\ Cl^-\right]} \longrightarrow (RO)_2P(=O)-SR' + RCl \qquad (3)$$

nucleophilic attack of chloride ion on the alkoxy group yields the thiol ester and alkyl chloride. According to this mechanism formation of the thiol ester should take place with retention of configuration around the phosphorus atom.

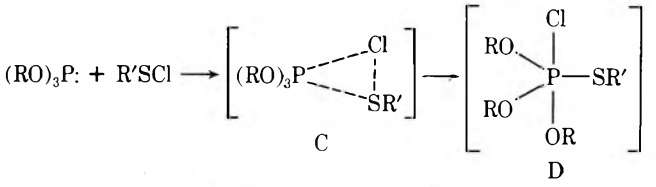
An alternative mechanism consists in nucleophilic attack of the phosphorus atom on the "electropositive" halogen atom[6] of the sulfenyl chloride molecule leading to the formation of a chlorophosphonium salt B. Displacement of

$$(RO)_3P: + \overset{\delta^+}{Cl}-\overset{\delta^-}{SR'} \longrightarrow \underset{B}{[(RO)_3\overset{+}{P}-Cl\ R'S^-]} \longrightarrow \left[(RO)_2\overset{+}{P}(O-R)-SR'\ Cl^-\right] \underset{A}{} \longrightarrow (RO)_2P(=O)-SR' + RCl + (R'S)_2 + (RO)_2P(=O)-Cl \qquad (4)$$

chloride ion by attack of mercaptide ion at phosphorus would convert intermediate B to the same "quasi-phosphonium salt" A which would then undergo the normal decomposition.

The stereochemical consequence of this mechanism is that the thiol ester should have a configuration opposite to that of the initial phosphite or be formed as a racemate. Inversion of configuration around the phosphorus atom would take place during the exchange of chlorine for the thioalkyl group in the chlorophosphonium salt B whereas chloride–chloride exchange in phosphonium salt B or the mercaptide–mercaptide exchange in phosphonium salt A would be responsible for racemization.

A third mechanism involving "biphilic" addition of the trivalent phosphorus atom to the S–Cl bond might also be considered[7] (eq 5). This would lead to the formation of a

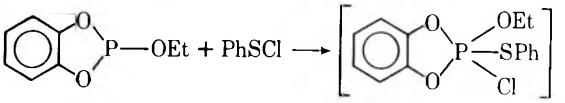


$$\rightleftharpoons [(RO)_3P{-}SR'\ Cl^-] \longrightarrow \text{products} \quad (5)$$

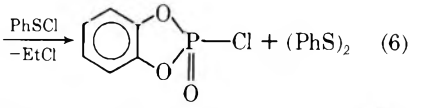
A

pentcovalent phosphorus intermediate D having the structure of a trigonal bipyramid in which the chlorine atom and the mercaptide group are probably situated in apical and equatorial positions, respectively. Intermediate D may be in equilibrium with the "quasi-phosphonium salt" A which then undergoes conversion to thiol ester and alkyl chloride. It should be mentioned that the pentacovalent intermediate D could be formed from either A or B. In this case the stereochemistry of the reaction would depend on the relative stability of D.[8] Rapid decomposition of D could lead to complete retention of configuration at phosphorus.

It should be emphasized that the involvement of a pentacovalent phosphorus intermediate has recently been established by Skowrońska, Mikołajczak, and Michalski[9] in the reaction between phenylsulfenyl chloride and 2-ethoxy-4,5-benzo-1,3,2-dioxaphospholane by means of ^{31}P NMR at −80 °C.



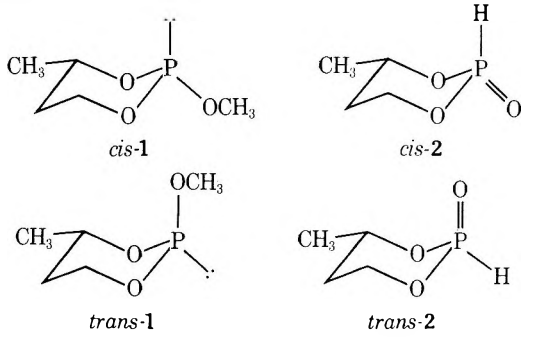
$\delta_{^{31}P}$ = + 19.3 ppm



(6)

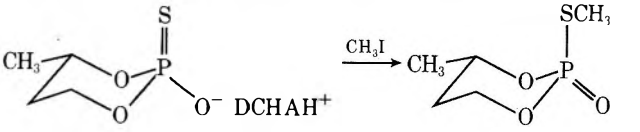
The possibility of investigating the steric course of the phosphite–sulfenyl chloride reaction appeared reasonable when diastereomerically pure geometrical isomers of cyclic trivalent phosphorus compounds,[10] optically active phosphonites, R(RO)P(O)H,[11] and esters of acids containing trivalent phosphorus, RR'POR,[12] became available. Cyclic trivalent phosphorus compounds are particularly convenient as models for such studies since they are configurationally stable and the diastereomeric reaction products are readily identifiable by nuclear magnetic resonance technique.

As convenient models we have used *cis*- and *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinanes (**1**)[13,14] and *cis*- and *trans*-2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (**2**).[14,15] The preparation and stereochemical behavior of these compounds have been described recently. In contrast to the conformationally homogeneous *trans*-**1** as well as *cis*-**2** and *trans*-**2**, the thermodynamically less stable phosphite *cis*-**1** has been shown [13]to exist as a mixture of conformers due to rapid ring flipping. However, in the conformation principally populated the ring methyl group is equatorial and this conformation is shown below.



In order to determine the steric course of reaction 1 it was first necessary to prepare by independent, unequivocal method *cis*- and *trans*-2-thiomethyl-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (**3**) which are the expected products of the reaction between the corresponding phosphites and methylsulfenyl chloride.

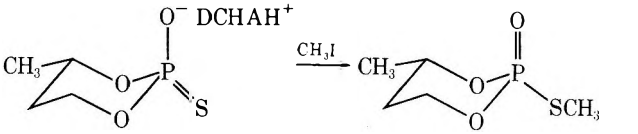
Synthesis, Configuration, and Conformation of *trans*- and *cis*-2-Methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (3). Diastereomeric thiol esters **3** were obtained by methylation of the diastereomeric dicyclohexylammonium salts of 2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphosphorinane (**4**) by means of methyl iodide. The configuration of *cis*- and *trans*-**4** has been previously established by Mikołajczyk and Łuczak.[14,16] Since the alkylation of thio acid salts takes place exclusively at the sulfur atom,[17] the configuration at phosphorus remains unchanged. Therefore, methylation of the trans thio acid salt gave a crystalline thio ester **3** (mp 76–78 °C) assigned the trans structure whereas the cis thio acid salt gave a liquid which was assigned the cis structure.



trans-**4**
mp 208–211 °C
$\delta_{^{31}P}$ −50.5 ppm

trans-**3**

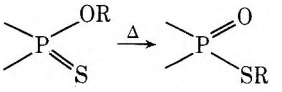
(7)



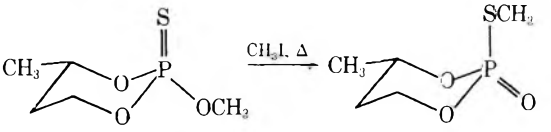
cis-**4**
mp 194–196 °C
$\delta_{^{31}P}$ −53.5 ppm

cis-**3**

Alternatively, thiol esters **3** may be prepared by the Pishschimuka reaction which involves the thermal isomerization of thionophosphates and is known to take place without configurational changes around the phosphorus atom.[18]



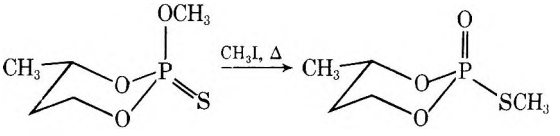
trans-2-Methoxy-2-thio-4-methyl-1,3,2-dioxaphosphorinane (**5**)[14,16] having a diastereomeric purity of 93% was heated with methyl iodide at 100 °C for 3 h in a sealed tube to give the same crystalline thiol ester **3** obtained from *trans*-**4**. Similarly the corresponding cis ester **5**[14,16] having a diastereomeric



trans-**5** (93% d.p.)

trans-**3** (100% d.p.)

(8)



cis-**5** (93% d.p.)

cis-**3** (87% d.p.)

purity of 93% gave the liquid thiol ester **3** accompanied by 13% of the isomeric *trans*-**3**. The slight decrease of diastereomeric purity in the latter reaction was probably due to the drastic reaction conditions since *cis*-**3** can suffer epimerization to the thermodynamically more stable crystalline isomer *trans*-**3**.

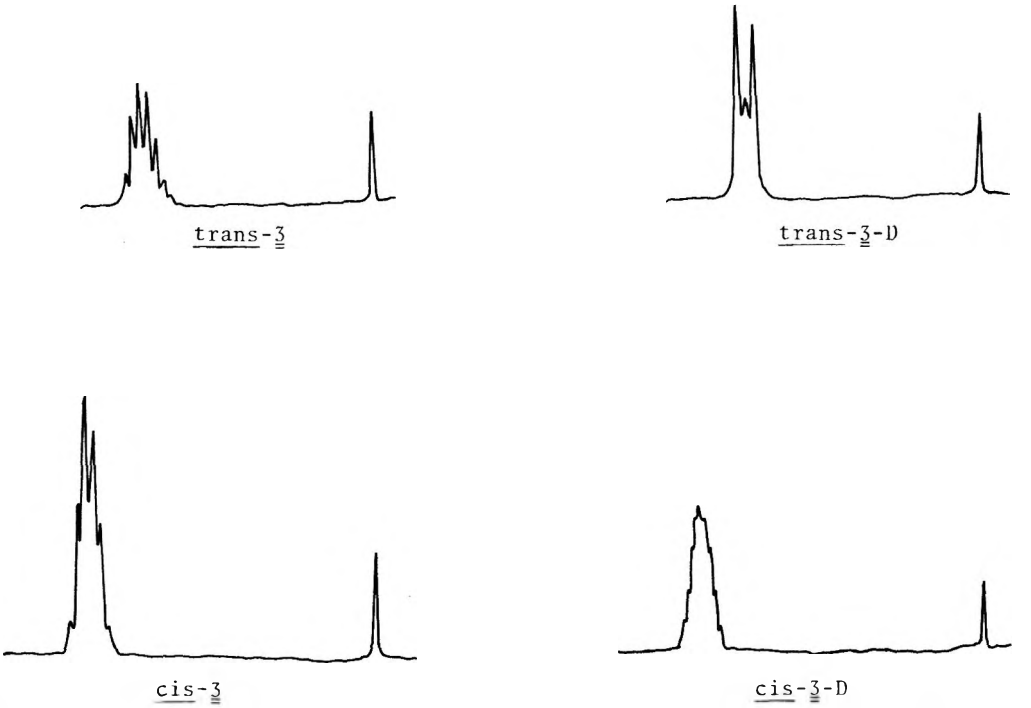


Figure 1. ^{31}P NMR spectra of *cis*- and *trans*-2-methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (**3**) and their *S*-trideuteriomethyl analogues.

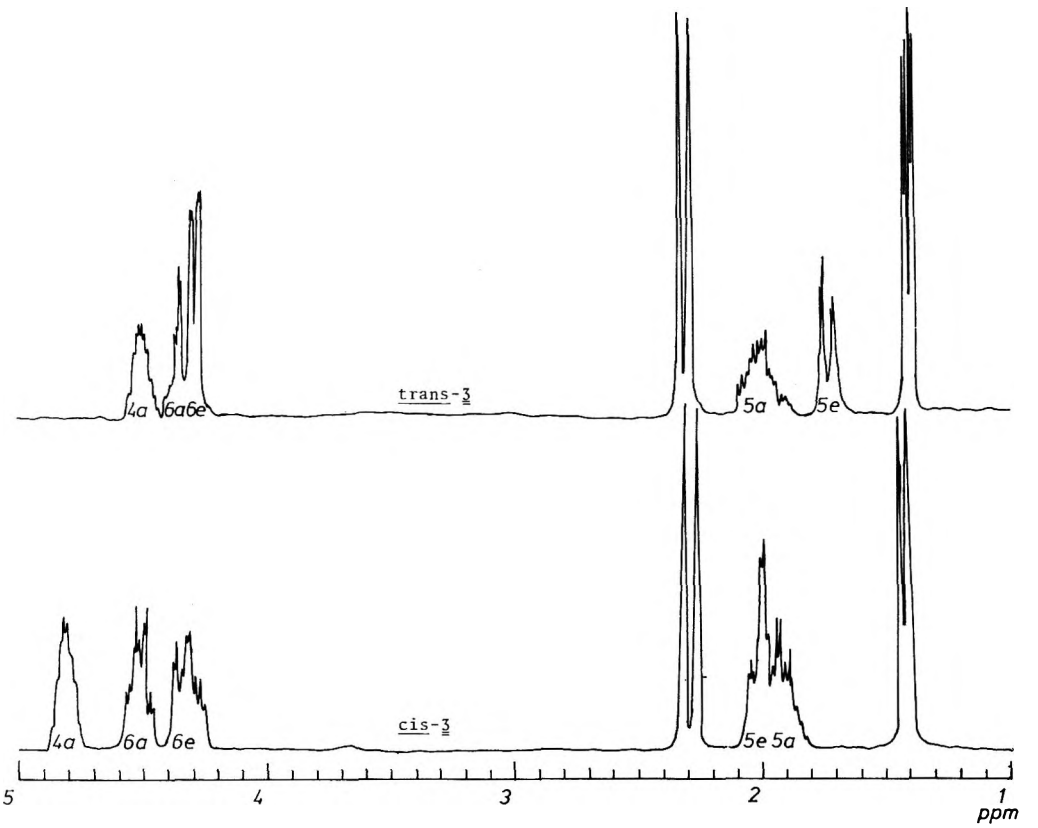
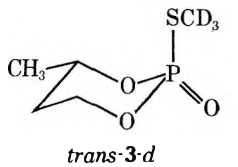
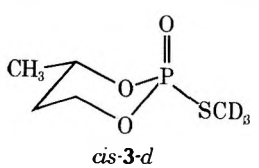


Figure 2. ^{1}H NMR spectra of the diastereomeric thiol esters (**3**) in CCl_4 at 300 MHz: top, *trans*-**3**; bottom, *cis*-**3**.

The structural assignments described were confirmed by means of ^{1}H and ^{31}P nuclear magnetic resonance studies, ir spectra, and dipole moment studies. The different spectral properties of the diastereomeric thiol esters **3** were used as a basis for determination of diastereomeric purity.



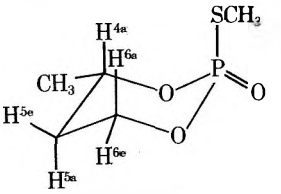
trans-**3**-*d*



cis-**3**-*d*

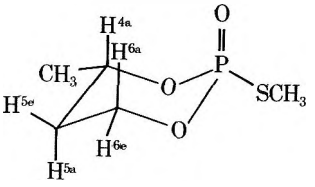
^{31}P NMR spectra of the two isomers show complex multiplets having chemical shifts at −21.0 and −25.8 ppm for *trans*-**3** and *cis*-**3**, respectively. In view of the fact that the spectra are complicated by splitting between phosphorus and the protons of the thiomethyl group the corresponding deuterated diastereomeric esters *trans*- and *cis*-**3**-*d* were prepared.

Table I. ^{1}H NMR Data for the Solid Isomer of 3 in Carbon Tetrachloride Solution at 300 MHz



Proton	Chemical shift, δ, ppm	Coupling constant (J, Hz) to						
		CH_3	5e	5a	6e	6a	4a	P
CH_3	1.42						6.30	2.20
5e	1.74			14.50	2.25	2.25	2.25	2.25
5a	2.01		14.50		5.80	11.50	11.50	0.50
6e	4.29		2.25	5.80		11.50		20.50
6a	4.35		2.25	11.50	11.50			2.25
4a	4.51	6.30						2.25
CH_3S	2.32							14.25

Table II. ^{1}H NMR Data for the Liquid Isomer of 3 in Carbon Tetrachloride Solution at 300 MHz



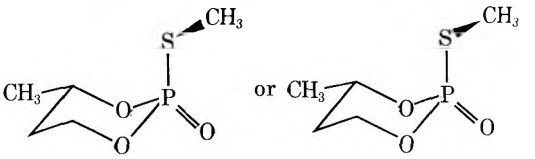
Proton	Chemical shift, δ, ppm	Coupling constant (J, Hz) to						
		CH_3	5a	5e	6e	6a	4a	P
CH_3	1.44						6.20	2.00
5a	1.92			14.70	4.50	10.80	10.50	0.60
5e	2.04		14.70		3.70	3.70	3.60	2.40
6e	4.33		4.50	3.70		11.40		18.00
6a	4.52		10.80	3.70	11.40			8.00
4a	4.82	6.20						4.50
CH_3S	2.32							15.65

The ^{31}P NMR spectrum of the deuterated crystalline isomer (*trans*-**3**-*d*) shows a double multiplet separated by about 20 Hz. According to previous observations[19] such a spectrum is characteristic of a dioxaphosphorinane ring having the chair conformation in which the methyl and phosphoryl groups are situated in equatorial positions. On the other hand the resonance signal for *cis*-**3**-*d* is a broad multiplet which is characteristic of dioxaphosphorinane systems having methyl and phosphoryl groups trans to one another.

More detailed information regarding the conformations of the cyclic thiol esters **3** was obtained by analysis of ^{1}H NMR spectra obtained at 300 Hz in carbon tetrachloride which are essentially first-order spectra (Figure 2). Chemical shifts and coupling constants derived from the spectra are given in Tables I and II.

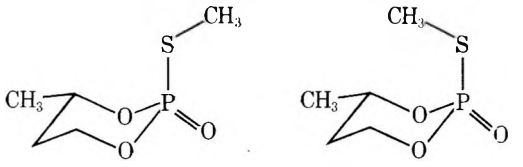
The ^{1}H NMR spectrum of the crystalline isomer consists of six multiplets. The doublet corresponding to three protons at δ 2.32 ppm and the double doublet at δ 1.42 ppm are ascribed to the thiomethyl group and the methyl group bonded to the C_4 carbon atom, respectively. The proton bonded to the C_4 carbon absorbs at lowest field, δ 4.51 ppm, as confirmed by irradiation at the frequency of the ring methyl group. The signals at δ 4.35 and 4.39 ppm correspond to protons bonded to the C_6 carbon atom whereas the single-proton split signal at δ 2.01 ppm having higher coupling constant and the single-proton split signal at δ 1.74 ppm having lower coupling constant corresponded to the axial and equatorial protons bonded to the C_5 carbon atom. The chemical shifts of the ring protons and, most importantly, the very pronounced differences between the long range ^{1}H–^{31}P couplings observed for the axial and equatorial protons of the dioxaphosphorinane[14,20] ring indicate that the ring in *trans*-**3** adopts the chair conformation with the methyl group in equatorial position. The high value of the coupling constant $^4J_{P-CH_3}$ (2.2 Hz) indicates that the methyl group is in the equatorial position whereas the low value of the coupling constant $^3J_{P-4a}$ (2.25 Hz) and the coupling constants J_{4a-5a} and J_{4a-5e} (11.5 and 2.25 Hz) which are typical for vicinal coupling constants J_{anti} and J_{gauche} in the chair conformation indicate that the proton at the C_4 carbon is in the axial position. Similarly the axial and equatorial protons at the C_6 carbon atom are split by phosphorus with low and high coupling constants $^3J_{P-6a}$ = 2.25 and $^3J_{P-6e}$ = 20.5 Hz. The coupling constants for phosphorus and the protons of the C_5 methylene group also show pronounced stereospecificity ($^4J_{P-5a}$ = 0.5 and $^4J_{P-5e}$ = 2.25 Hz).

Since the relative positions of the methyl group and the phosphoryl group in the crystalline isomer follow unambiguously from the method of synthesis it can be assumed that the phosphoryl group occupies the equatorial position whereas the *S*-methyl group is axial. It should be mentioned that low temperature ^{1}H NMR spectra (60 MHz) showed no changes down to −60 °C which is interpreted to mean that *trans*-**3** exists only in one chair conformation. Taking into account the possible existence of rotational isomers due to rotation of the



trans-**3**-*gauche*

μ_{calcd} = 5.59 D



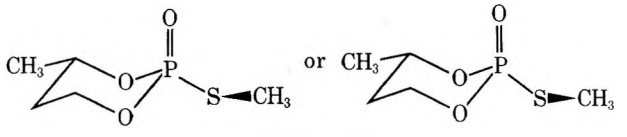
trans-**3**-*syn* μ_{calcd} = 5.01 D

trans-**3**-*anti* μ_{calcd} = 7.05 D

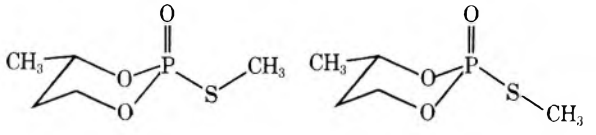
S-methyl group around the P–S bond and our dipole moment studies[21] (μ 5.63 D for *trans*-**3**) we come to the final conclusion that *trans*-**3** exists in a single chair conformation in which the methyl and phosphoryl groups are in equatorial positions whereas the *S*-methyl group is in a position gauche with respect to the phosphoryl group.

Analysis of proton chemical shifts and coupling constants for the liquid isomer *cis*-**3** as shown in Table II leads to the conclusion that the dioxaphosphorinane ring in this isomer also exists in chair conformation with the C_4 methyl group equatorial and the phosphoryl group axial, i.e., that the only difference between *cis*- and *trans*-**3** is the configuration at the phosphorus atom. In agreement with observations reported by Hall and Malcolm[22] the value of the coupling constant for the ring methyl protons with phosphorus obtained in our work ($^4J_{P-CH_3}$ = 2 Hz) is characteristic of an anti relationship between the bond from ring to ring methyl and the endocyclic O–P bond, i.e., it is characteristic of an equatorial ring methyl group in a chair-shaped ring. However, in this case the coupling constant between phosphorus and the proton bonded to the C_4 carbon is 4.50 Hz and that between phosphorus and the protons bonded to the C_6 carbon atom are 18 and 8 Hz. The last value corresponds to coupling with an axial proton but is too high for such coupling. This could be due either to some flattening of dioxaphosphorinane ring in *cis*-**3** or to a slight contribution of the conformer resulting from ring inversion. However, investigation of the temperature dependence of the ^{1}H NMR spectra at 60 MHz in the range from 60 to −60 °C did not reveal any changes in chemical shifts or coupling constants for the C_4 methyl group and the thiomethyl group. Although only a lack of change down to −100 °C would be considered convincing proof for the absence of conformational equilibrium, in our opinion the observed increase of the values of $^3J_{P-4a}$ and $^3J_{P-6a}$ can tentatively be ascribed to ring deformation, particularly in view of the fact that the axial phosphoryl group and the equatorial thiomethyl group are situated in positions opposite to those preferred for these substituents in the 1,3,2-dioxaphosphorinane system.[23,24]

The experimentally determined value of the dipole moment of *cis*-**3** (μ 5.06 D) probably corresponds to a mixture of rotational isomers *cis*-**3**-*gauche* and *cis*-**3**-*anti* in which the latter predominates.



cis-**3**-*gauche* μ_{calcd} = 3.81 D

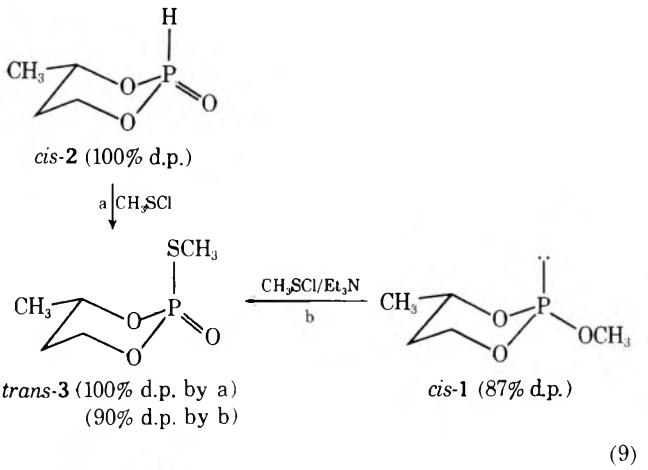


cis-**3**-*syn* μ_{calcd} = 3.10 D

cis-**3**-*anti* μ_{calcd} = 5.42 D

Reaction of Sulfenyl Chlorides with Cyclic Trivalent Phosphorus Compounds. Knowledge of the configuration of the geometric isomers of 2-methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**3**) was used to determine the steric course of the reactions between methylsulfenyl chloride and diastereomeric phosphites **1** and **2**.

It was found that reaction between the more stable isomer *cis*-**2** and methylsulfenyl chloride (route a) at 0 °C in ether or benzene gave *trans*-2-thiomethyl-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**3**). The same product (*trans*-**3**) was also formed by reaction of the thermodynamically less stable isomer *cis*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinane (**1**) with methylsulfenyl chloride (route b). In this case the reaction was carried out in the presence of a small amount of triethylamine which was used to scavenge traces of hydrogen chloride present in the sulfenyl chloride. The reaction was

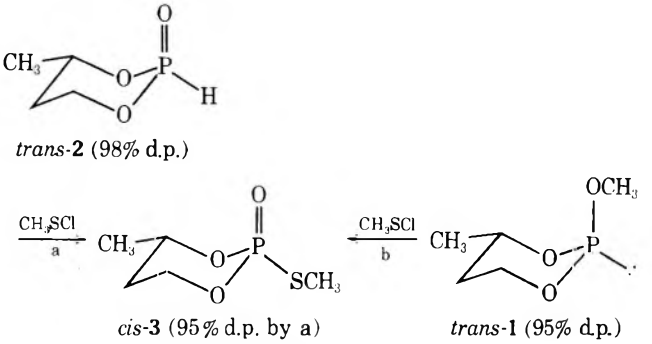


cis-**2** (100% d.p.)

trans-**3** (100% d.p. by a) (90% d.p. by b)

cis-**1** (87% d.p.)

(9)



trans-**2** (98% d.p.)

cis-**3** (95% d.p. by a) (95% d.p. by b)

trans-**1** (95% d.p.)

completely stereospecific. When the reaction was performed in the absence of triethylamine the diastereomeric purity of the resulting *trans*-**3** was lower because of epimerization of the precursor *cis*-**1** caused by traces of hydrogen chloride present in the reaction mixture.[13,14]

Similarly reaction of methylsulfenyl chloride with the thermodynamically less stable phosphite *trans*-**2** and the more stable phosphite *trans*-**1** were completely stereospecific. In both cases the product of reaction was the liquid thiol ester *cis*-**3**.

Since the geometrical structures of the initial phosphites **1** and **2** and the resulting thiol esters **3** are known, the results shown demonstrate that the reactions shown take place with complete retention of configuration at phosphorus.

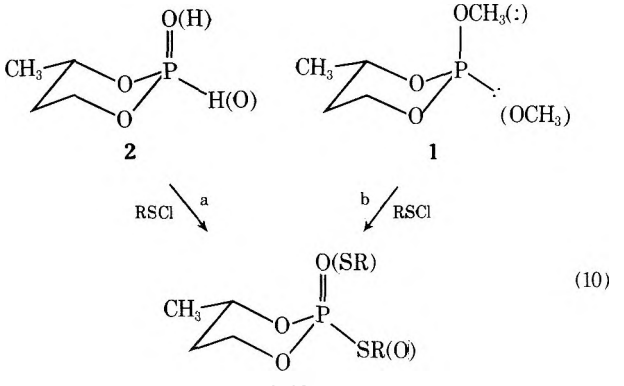
In order to determine whether the particular alkyl or aryl group present in the sulfenyl chloride has an effect on the steric course of the reaction we investigated reactions involving various sulfenyl chlorides. In all cases stereospecific formation of 2-thioalkyl(thioaryl)-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes was observed with retention of configuration at the phosphorus atom (eq 10).

Physical and chemical properties of reaction products are collected in Table III and the corresponding spectral data (^{1}H, ^{31}P NMR, and ir) in Table IV.

Reactions involving 2,4-dinitrophenylsulfenyl chloride require additional comments. We have found that conversion

Table III. Preparation and Physical Properties of *cis*- and *trans*-2-Alkylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes

No.	R	Thiol ester	Bp, °C (mmHg); mp, °C	n^{20}D	Synthetic route	Yield, %	Elemental analyses: Found C	H	P	Calcd C	H	P
3	CH_3	Trans	76–78 (from benzene–cyclohexane)		a	82.3	33.05	6.08	17.42	32.96	6.09	17.00
					b	66.0	33.10	6.20	17.05			
		Cis	90 (0.05)	1.4992	a	67.7	33.33	6.17	17.32			
					b	77.8	33.10	6.00	17.08			
6	CH_3CH_2	Trans	118 (0.1)	1.4937	a	90.3	37.00	6.84	16.23	36.73	6.68	15.79
		Cis	82–84 (0.01)	1.4880	a	51.0	36.88	6.80	15.80			
7	$CH_3CH_2—CH_2$	Trans	107 (0.01)	1.4912	a	62.0	40.13	7.26	14.95	39.98	7.19	14.73
		Cis	91–93 (0.02)	1.4840	a	62.0	39.65	7.20	14.38			
8	$(CH_3)_2CH$	Trans	105 (0.02)	1.4886	a	76.2	40.00	7.20	15.13	39.98	7.19	14.73
		Cis	90 (0.02)	1.4880	a	67.0	39.70	7.54	15.21			
9	C_6H_5	Trans	103–104.5 (from benzene–cyclohexane		a	96.0	48.90	5.32	13.00	49.13	5.36	12.68
					b	77.0	48.64	5.20	13.11			
		Cis	68–69.5 (from benzene–ether)		a	78.0	49.17	5.36	12.78			
					b	49.0	50.21	5.79	12.83			
10	2,4-$(NO_2)_2C_6H_4$	Trans	125–127 (from dimethoxyethane–petroleum ether)		a	85.6	35.97	3.48	9.51	35.96	3.31	9.27
		Cis			a		36.47	3.40	8.76			

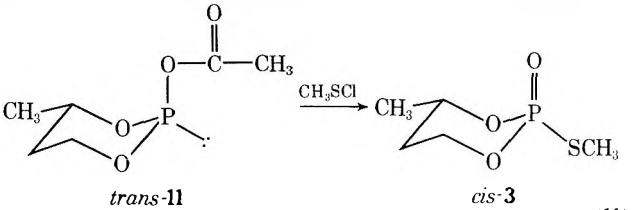


6, R = Et
7, R = *n*-Pr
8, R = *i*-Pr
9, R = C_6H_5[25]
10, R = 2,4-$(NO_2)_2C_6H_4$

of *cis*- and *trans*-**2** into the corresponding thiol derivatives **10** takes place in high yield with complete retention of configuration. However, in contrast to the thermodynamically more stable *trans*-**10** the corresponding cis isomer could not be isolated in an analytically pure state. This difficulty could be a consequence of the instability of *cis*-**10** and its exceptional sensitivity to moisture which is undoubtedly due to the presence of the 2,4-dinitrophenoxy group which is expected to undergo ready nucleophilic displacement from the phosphorus atom. The same effect is probably responsible for the fact that reaction between *trans*-**1** and 2,4-dinitrophenylsulfenyl chloride is not completely stereospecific and yields 22% of the trans isomer in addition to the expected *cis*-**10**.

The NMR and ir spectral data obtained for diastereomeric thiol esters **3** and **6–10** (Table IV) reveal several interesting relationships between the configuration at phosphorus and certain spectroscopic constants. Thus all of the trans thiol isomers absorb in ^{31}P NMR at a higher field than the corresponding cis isomers. Similarly in ^{1}H NMR the coupling constants between phosphorus and the protons of the ring methyl groups of the trans isomers are always higher than those of the cis isomers. However, in the case of the cis isomers the coupling is always greater than 1 Hz indicating that the ring methyl group should be equatorial even in these cases. As expected, the infrared absorption of the phosphoryl group (P=O) of the trans isomers appears at a higher wavenumber than that of the corresponding cis isomers thereby confirming the correctness of our configurational assignments.[26]

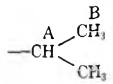
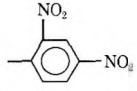
In extension of this study we examined the reaction between methylsulfenyl chloride and *trans*-2-acetoxy-4-methyl-



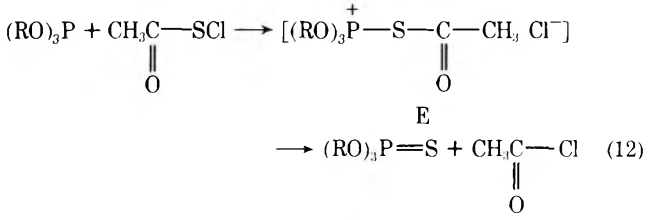
1,3,2-dioxaphosphorinane (**11**) the structure of which has been unambiguously established by Nifantiev.[27] Formation of *cis*-**3** indicates that the configuration at phosphorus in this reaction is also completely retained.

Michalski and Skowrońska[28] have shown that acetylsulfenyl chloride, unlike simple sulfenyl chlorides, reacts with trivalent phosphorus esters to afford the corresponding thionophosphates resulting from the simple addition of sulfur. It is assumed that during the reaction an intermediate phosphonium

Table IV. Spectroscopic Properties of *cis*- and *trans*-2-Alkylthio(arylthio)-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes

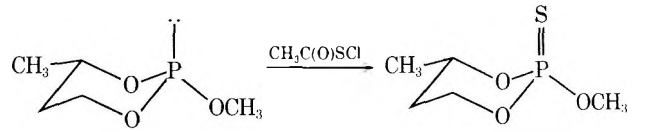
Thiol ester			NMR, δ, ppm			IR[c]	
No.	R		^{1}H (J, Hz)[a]	$^4J_{CH_3-P}$	^{31}P[b]	ν(P=O)	ν (other)
3	$-CH_3$	Trans	1.42 (dd, 3 H, $^3J_{CH_3-H}$ = 6.3, $^4J_{CH_3-P}$ = 2.2 Hz); 1.87 (m, 2 H); 2.31 (d, 3 H, $^3J_{CH_3-P}$ = 14.25 Hz); 4.38 (m, 3 H)	2.2	−21.0	1270 vs	1253 vs (P=O) 595 vs (P–S(C))
		Cis	1.44 (dd, 3 H, $^3J_{CH_3-H}$ = 6.2, $^4J_{CH_3-P}$ = 2.0 Hz); 1.98 (m, 2 H); 2.31 (d, 3 H, $^3J_{CH_3-P}$ = 15.65 Hz); 4.56 (m, 3 H)	2.0	−25.8	1260 vs	563 vs (P–S(C))
6	A B $-CH_2-CH_3$	Trans	1.13 (dd, 3 H, $^3J_{CH_3-H}$ = 6.6, $^4J_{CH_3-P}$ = 2.4 Hz); 1.25 (t, 3 H_B, $J_{H_B-H_A}$ = 7.8 Hz); 2.8 (m, 2 H_A)	2.4	−18.5	1280 vs	1265 vs (P=O) 565 vs, 600 vs (P–S(C))
		Cis	1.14 (dd, 3 H, $^3J_{CH_3-CH}$ = 6.75, $^4J_{CH_3-P}$ = 1.8 Hz); 1.22 (t, 3 H_B, $J_{H_B-H_A}$ = 7.8 Hz); 2.8 (m, 2 H_A)	1.8	−22.8	1255 vs	1280 v (P=O) 565 vs, 600 v (P–S(C))
7	A B C $-CH_2-CH_2-CH_3$	Trans	0.97 (dgt, 3 H_C, $J_{H_B-H_C}$ = 7.5 Hz); 1.65 (m, 2 H_B); 1.3 (dd, 3 H, $^3J_{CH_3-H}$ = 6.75, $^4J_{CH_3-P}$ = 2.4 Hz); 2.84 (dt, 2 H_A, $J_{H_A-H_B}$ = 7.2 Hz)	2.4	−18.8	1283 vs	1253 s (P=O) 600 v (P–S–(C))
		Cis	0.94 (dgt, 3 H_C, $J_{H_B-H_C}$ = 7.5 Hz); 1.28 (dd, 3 H, $^3J_{CH_3-H}$ = 6.75, $^4J_{CH_3-P}$ = 1.8 Hz); 1.65 (m, 2 H_B); 2.84 (dt, 2 H_A, $J_{H_A-H_B}$ = 7.2 Hz)	1.8	−22.6	1260 vs	1273 vs (P=O)
8		Trans	1.12 (dd, 3 H, $^3J_{CH_3-H}$ = 6.6, $^4J_{CH_3-P}$ = 2.4 Hz); 1.31 (d, 6 H_B, $J_{H_A-H_B}$ = 7.2 Hz); 3.57 (d sep, 1 H_A, $J_{H_A-H_B}$ = 7.2, $^3J_{P-H}$ = 12 Hz)	2.4	−16.8	1285 vs	1252 s (P=O)
		Cis	1.16 (dd, 3 H, $^3J_{CH_3-H}$ = 6.6, $^4J_{CH_3-P}$ = 1.8 Hz); 1.31 (d, 6 H_B, $J_{H_A-H_B}$ = 7.8 Hz); 3.55 (d sep, 1 H_A, $J_{H_A-H_B}$ = 7.2, $^3J_{P-H}$ = 12.6 Hz)	1.8	−21.0	1260 vs	1278 vs (P=O)
9		Trans	1.01 (dd, 3 H, $^3J_{CH_3-H}$ = 6.6, $^4J_{CH_3-P}$ = 2.5 Hz); 7.4 (m, 5 H, aromatic)	2.5	−11.9	1282 vs	1254 s (P=O) 558 vs, 592 vs (P–S(aromatic))
		Cis	0.89 (dd, 3 H, $^3J_{CH_3-H}$ = 6.75, $^4J_{CH_3-P}$ = 2.1 Hz); 7.4 (m, 5 H, aromatic)	2.1	−15.5	1272 vs	1250 m (P=O) 561 vs, 610 vs (P–S–C(aromatic))
10		Trans	0.80 (dd, 3 H, $^3J_{CH_3-CH}$ = 6.25, $^4J_{CH_3-P}$ = 2.75 Hz)	2.75	−7.0	1290 vs	1248 v (P=O)
		Cis	0.88 (dd, 3 H, $^3J_{CH_3-H}$ = 6.5, $^4J_{CH_3-P}$ = 1.5 Hz)	1.5	−8.2		

[a] Measured at ambient probe temperatures, JEOL JNM-C60-HL spectrometer. Chemical shifts downfield from Me_4Si as internal standard. Abbreviations used: s, singlet; d, doublet; t, triplet; dt, double triplet, dgt, degenerate triplet; sep, septet; d sep, double septet; m, multiplet. [b] Measured with a JEOL JNM-C-60 HL operating at 24.3 MHz. Chemical shifts downfield from external 85% H_3PO_4. Heteronuclear spin decoupler JNM-SD-HC was used for precise chemical shift determination. [c] Infrared spectra were taken on a UR-10-Zeiss or Spectromom 2000 infrared spectrophotometers. Abbreviations used: vs, very strong; s, strong; m, middle.



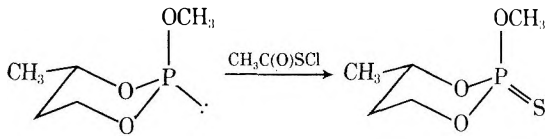
salt E is formed which subsequently suffers attack of chloride ion at the most electrophilic site, namely the carbon atom.

Confirmation of the proposed mechanism and investigation of the steric course of the reaction by means of diastereomeric cyclic phosphites was of interest. For this purpose *cis*- and



cis-**1** (92% d.p.) *trans*-**5** (93% d.p.)

(13)



trans-**1** (92% d.p.) *cis*-**5** (93% d.p.)

trans-**1** were treated with acetylsulfenyl chloride in ether at 0 °C. Diastereomeric purities of both reactants and products as determined by gas chromatography and ^{31}P NMR spectra are shown.

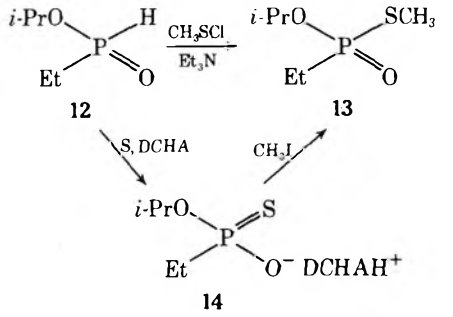
Treatment of *cis*-**1** containing 8% of the trans isomer with acetylsulfenyl chloride gave trans thionophosphate **5** containing 7% of the corresponding cis isomer. Analogously *trans*-**1** having a diastereomeric purity of 90% gave cis thionophosphate **5** containing 7% of the trans isomer. Thus in this case also addition of sulfur takes place with complete retention of configuration at phosphorus. From a preparative point of view it is noteworthy that this reaction is carried out under very mild conditions.

All of our results corroborate the hypothesis that cyclic phosphites react with a variety of sulfenyl chlorides according to the mechanism involving the intermediate "quasi-phosphonium salt" such as A or E. Further reaction depends on the exact nature of this species. The results of the stereochemical studies do not exclude the possible involvement of the pentacovalent intermediate D which would decompose to the final products with retention of configuration. Intermediates A and D could be in equilibrium with one another. It can be assumed that the reaction of sulfenyl chlorides with phosphites such as **2**, in which the reactive species is phosphite form, >P̈–OH, occurs according to a similar mechanism.

Our stereochemical results exclude a mechanism involving nucleophilic attack of phosphorus on "electropositive" chlorine to give initially the chlorophosphonium salt B. It should be emphasized that even in the reactions involving 2,4-dinitrophenylsulfenyl chloride we observed retention at phosphorus. In the case of this sulfenyl chloride nucleophilic attack on chlorine is expected to be probable in view of stabilization of the negative charge on sulfur by the dinitrophenyl substituent.

Further stereochemical studies are planned on the reactions of phosphites with trichloromethyl- and trifluoromethylsulfenyl chloride since in these cases phosphorus chloroanhydrides and disulfides are formed in addition to thiol esters.

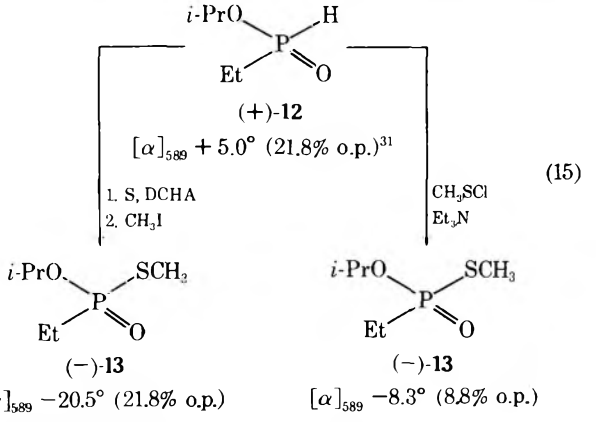
Reaction of Methylsulfenyl Chloride with Optically Active *O*-Isopropyl Ethylphosphinate. It was shown above that reaction of cyclic trivalent phosphorus compounds with a variety of sulfenyl chlorides takes place with retention of configuration at phosphorus. Since steric course and mechanism of reactions of cyclic phosphoroorganic compounds are often different from those of acyclic analogues[29] we have investigated the reaction of methylsulfenyl chloride with optically active *O*-isopropyl ethylphosphinate (**12**) the two optical forms of which were obtained by partial resolution of the racemate via β-cyclodextrin inclusion complexes according to the procedure of Benschop and Van den Berg.[30] All reactions carried out with optically active phosphinates **12** were pre-



(14)

ceded by preliminary experiments with the racemic material. Thus reaction of racemic **12** with methylsulfenyl chloride carried out at 0 °C in the presence of triethylamine gave a good yield of *O*-isopropyl *S*-methyl ethylphosphonothioate (**13**). The same ester **13** was obtained by addition of elemental sulfur to compound **12** in the presence of dicyclohexylamine followed by methylation of the resulting dicyclohexylammonium salt (**14**) by means of methyl iodide.

We have carried out a similar cycle of reactions using the optically active forms of **12.** Phosphinate (+)-**12** having specific rotation $[\alpha]_{589}$ +5.0° and methylsulfenyl chloride gave (−)-**13** having specific rotation $[\alpha]_{589}$ −8.3°. Ester **13** having the same configuration but a much higher specific rotation,



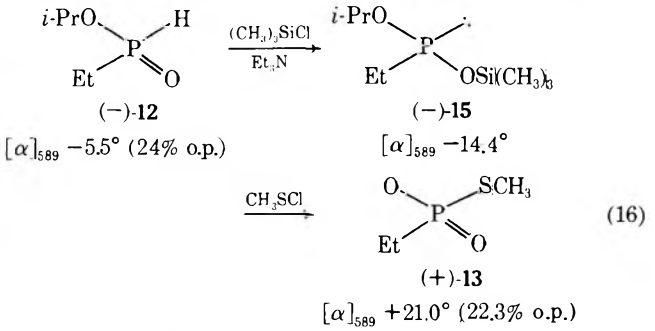
(15)

$[\alpha]_{589}$ −20.5°, is formed as a result of the addition of sulfur to a sample of (+)-**12** having $[\alpha]_{589}$ +5.0° in the presence of dicyclohexylamine followed by methylation of the resulting salt. Since addition of sulfur and methylation of the thio acid anion occur with retention of configuration at phosphorus, the thiol ester (−)-**13** and the initial phosphinate (+)-**12** have the same configuration. Thus reaction of methylsulfenyl chloride with optically active **12** takes place with predominant retention of configuration.

It should be mentioned that the ester **13** formed when the reaction is carried out in the absence of triethylamine is nearly completely racemic. This is probably due to racemization of the starting material **12** caused by hydrogen chloride generated in the reaction, according to the mechanism proposed by Emmick and Letsinger[33] for the racemization of secondary phosphine oxides. Although the use of triethylamine increases the stereospecificity of the reaction of methylsulfenyl chloride with optically active phosphinate **12**, it does not completely inhibit racemization. This is most likely due to the formation and racemization of an intermediate mesomeric phosphonate

anion (>P̈–O⁻ ↔ >P̈=O) which may be formed from **12** by interaction with triethylamine.

Since the optical sensitivity of the >P(O)H system to acids and bases makes it difficult to interpret the steric course of the reaction with methylsulfenyl chloride, we substituted the optically active trimethylsilyl derivative **15** for phosphinate



(−)-**12** $[\alpha]_{589}$ −5.5° (24% o.p.)

(−)-**15** $[\alpha]_{589}$ −14.4°

(+)-**13** $[\alpha]_{589}$ +21.0° (22.3% o.p.) (16)

12. Benschop[34] has shown that silylation of phosphonates occurs on oxygen and causes no change in configuration at phosphorus.

As expected, reaction of (−)-*O*-isopropyl *O*-trimethylsilyl ethylphosphonite (**15**), $[\alpha]_{589}$ −14.4° [prepared from (−)-**12**, $[\alpha]_{589}$ −5.5°], with methylsulfenyl chloride gave optically active ester (+)-**13** with $[\alpha]_{589}$ +21.0°. Comparison of the specific rotation of the ester prepared by this way with that of the ester obtained by addition of sulfur demonstrates that the reaction takes place with almost complete retention of configuration at phosphorus. Therefore, it is clear that the reactions of simple sulfenyl chlorides with both cyclic and acyclic trivalent phosphorus compounds follow the same steric course, namely complete retention of configuration around the phosphorus atom in the thiol ester product.

Experimental Section

All melting and boiling points are uncorrected. NMR spectra were recorded on a Tesla BS-487C 80-MHz spectrometer or JEOL JNM-C-60 HL 60-MHz spectrometer using Me_4Si as an internal standard. The ^{31}P magnetic resonance data were obtained on a JEOL JNM-C-60 HL spectrometer operating at 24.3 MHz. Proton decoupling was accomplished with heteronuclear spin decoupler JNM-SD-HC. Ir spectra were measured on Zeiss-UR-10 or Spectromom 2000 spectrophotometers as KBr disks for solids and pressed films for liquids. GLC analysis was carried out with a Varian Aerograph Model 1520 flame ionization gas chromatograph. Optical activity measurements were made with a Perkin-Elmer 141 photopolarimeter (sensitivity ±0.002°) or with a Hilger and Watts polarimeter (sensitivity ±0.01°). All solvents used were purified according to standard procedures. All reactions involving trivalent phosphorus compounds were carried out under an atmosphere of dry nitrogen.

Synthesis of *trans*-2-Methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (3). To a solution of the dicyclohexylammonium salt of *trans*-2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphosphorinane (**4**,[14] 3.5 g, 0.01 mol) in 50 ml of benzene an excess of methyl iodide was added. The reaction mixture was allowed to stand at room temperature overnight. The precipitated dicyclohexylammonium iodide was filtered off. The benzene solution was evaporated to afford the crude thiol ester *trans*-**3**. Crystallization from benzene–ether gave 1.4 g (78%) of the pure *trans*-**3**, mp 76–78 °C. Physical and spectroscopic properties are given in Tables I, III, and IV.

Synthesis of *cis*-2-Methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (3). To a suspension of the dicyclohexylammonium salt of *cis*-2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphosphorinane (**4**,[14] 3.5 g, 0.01 mol) in benzene (50 ml) an excess of methyl iodide was added. The reaction mixture was stirred at room temperature for 24 h and dicyclohexylammonium iodide was then filtered off. Evaporation of filtrate gave the crude *cis*-**3** as an oil which was distilled to afford the pure *cis*-**3**: 1.5 g (82%); bp 90 °C (0.05 mmHg); $n^{20}D$ 1.4992; mp 17 °C. Spectroscopic data of the product are given in Tables II and IV.

cis-**3**-*d* and *trans*-**3**-*d* were prepared in the same manner as described above using trideuteriomethyl iodide.

Isomerization of *trans*-2-Methoxy-2-thio-4-methyl-1,3,2-dioxaphosphorinane (5) to *trans*-3. *trans*-**5** (93% diastereomeric purity) (1.5 g, 0.00825 mol) and methyl iodide were heated in a sealed tube for 3 h at 100 °C. The reaction mixture was then dissolved in benzene and the benzene solution was washed with a 5% aqueous solution of Na_2SO_3 and water. After removal of the solvent crystallization of the residue from benzene–ether yielded 0.5 g (33%) of the diastereomerically pure *trans*-**3**, mp 76–78 °C.

Isomerization of *cis*-2-Methoxy-2-thio-4-methyl-1,3,2-dioxaphosphorinane (5) to *cis*-3. Essentially the same procedure as above yielded from 1.5 g (0.00825 mol) of *cis*-**5** (93% diastereomeric purity) 0.8 g (53.4%) of the 87% diastereomerically pure (^{31}P NMR and GLC assay) *cis*-**3**, bp 90 °C (0.5 mmHg).

General Procedure for Reaction of Alkyl- and Arylsulfenyl Chlorides with Diastereomeric Phosphites 1 and 2. To a stirred solution of 0.03 mol of *cis*- and *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinane (**1**) or *cis*- and *trans*-2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**2**) in benzene (30 ml), sulfenyl chloride (0.035 mol) in 10 of benzene was added at 0–5 °C. The reaction mixture was stirred at room temperature for 2 h. After removal of solvent the residue was distilled or crystallized to give thioesters which were analyzed by means of ^1H, ^{31}P NMR, and ir spectroscopy and GLC. Yields of the analytically pure products and their physical and spectroscopic properties are collected in Tables III and IV.

In the case of *cis*-**1** as substrate the reaction was carried out in the presence of triethylamine (0.006 mol).

Reaction of *trans*-2-Acetoxy-4-methyl-1,3,2-dioxaphosphorinane (11) with Methylsulfenyl Chloride. Methylsulfenyl chloride (1.65 g, 0.02 mol) in ether (5 ml) was added at 0 °C to a solution of *trans*-**11** (3.56 g, 0.02 mol) in ether (20 ml). The reaction mixture was stirred at room temperature for 1 h. Removal of ether afforded the crude, diastereomerically pure *cis*-2-methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**3**) which was isolated by distillation: 2.8 g (77%); bp 98–102 °C (0.2 mmHg); $n^{20}D$ 1.4992; $\delta_{^{31}P}$ −25.8 ppm.

Reaction of *cis*-2-Methoxy-4-methyl-1,3,2-dioxaphosphorinane (1) with Acetylsulfenyl Chloride. To phosphite *cis*-**1** (92% d.p., 1.5 g, 0.01 mol) in ether (30 ml) acetylsulfenyl chloride (1.1 g, 0.01 mol) in ether (5 ml) was added at −5 °C. After stirring at room temperature for 1 h and removal of ether the reaction product was distilled to give 1.3 g (71.5%) of *trans*-2-methoxy-2-thio-4-methyl-1,3,2-dioxaphosphorinane (**5**) having 93% of diastereomeric purity (^{31}P NMR and GLC assay): bp 78–80 °C (0.3 mmHg); $n^{20}D$ 1.4892; $\delta_{^{31}P}$ −65.0 ppm (neat).

Reaction of *trans*-2-Methoxy-4-methyl-1,3,2-dioxaphosphorinane (1) with Acetylsulfenyl Chloride. Reaction of *trans*-**1** (90% d.p., 1.5 g, 0.01 mol) with acetylsulfenyl chloride carried out under the same conditions gave after distillation 1.4 g (77%) of *cis*-**5** (93% d.p.): bp 76–78 °C (0.03 mmHg); $n^{20}D$ 1.4930; $\delta_{^{31}P}$ −63.0 ppm (neat).

Reaction of (+)-*O*-Isopropyl Ethylphosphinate (12) with Methylsulfenyl Chloride. To a solution of (+)-**12**, $[\alpha]_{589}$ +5.0° (1.9 g, 0.0145 mol), in 50 ml of benzene, triethylamine (1.47 g, 0.0145 mol) and then methylsulfenyl chloride (1.2 g, 0.0145 mol) were added at 0 °C. The reaction mixture was stirred for 3 h and the precipitated triethylammonium chloride was filtered off. Removal of benzene and distillation of the residue gave 1 g (40%) of (−)-*O*-isopropyl *S*-methyl ethylphosphonothioate (**13**): $[\alpha]_{589}$ −8.3° (c 13.49, benzene); bp 69–70 °C (2 mmHg); $n^{20}D$ 1.4595; ^1H NMR (benzene) δ 4.78 (d sep, 1 H, $^3J_{CH-CH_3}$ = 6.4, $^3J_{CH-P}$ = 9.6 Hz), 2.17 (d, 3 H, $^3J_{CH_3-P}$ = 12.6 Hz), 1.72 (m, 2 H), 1.2 (m, 9 H). Anal. Calcd for $C_6H_{15}O_2PS$: C, 39.58; H, 8.29; P, 17.00. Found: C, 39.84; H, 8.43; P, 17.17.

Starting from (−)-**12**, $[\alpha]_{589}$ −4.0°, and methylsulfenyl chloride (+)-**13**, $[\alpha]_{589}$ +12.4° (c 9.81, benzene), was obtained.

Synthesis of (−)-*O*-Isopropyl *S*-Methyl Ethylphosphonothioate (13) from (+)-*O*-Isopropyl Ethylphosphinate (12) via Sulfur Addition and Methylation. To a mixture of (+)-**12**, $[\alpha]_{589}$ +5.0° (2 g, 0.0147 mol), and dicyclohexylamine (2.66 g, 0.0147 mol) in ether (50 ml) was added sulfur (0.47 g, 0.0147 mol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The precipitated dicyclohexylammonium salt of *O*-isopropyl ethylphosphonothioate (**14**) was filtered off and dissolved in benzene (50 ml). The benzene solution was treated with an excess of methyl iodide and the reaction mixture was allowed to stand at 40 °C for 5 h. The precipitated dicyclohexylammonium iodide was filtered off, the benzene solution evaporated, and the residue distilled to give 1.4 g (52.5%) of (−)-**13**: $[\alpha]_{589}$ −20.5°; bp 63 °C (1.7 mmHg); $n^{20}D$ 1.4605. Anal. Calcd for $C_6H_{15}O_2PS$: C, 39.58; H, 8.29; P, 17.00. Found: C, 40.06; H, 8.80; P, 17.38.

Reaction of (+)-**12**, $[\alpha]_{589}$ +5.7°, according to the same procedure gave (−)-**13**, $[\alpha]_{589}$ −23.5°.

Synthesis of (+)-*O*-Isopropyl *S*-Methyl Ethylphosphonothioate (13) from (−)-*O*-Isopropyl Ethylphosphinate (12) via

(−)-*O*-Isopropyl *O*-Trimethylsilyl Ethylphosphonite (15). To a solution of (−)-**12**, $[\alpha]_{589}$ −5.5° (3.4 g, 0.025 mol), in benzene (50 ml), triethylamine (3.78 g, 0.0375 mol) and then trimethylchlorosilane (4.06 g, 0.0375 mol) were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h and the precipitated triethylammonium chloride filtered off. The filtrate was cooled to 0 °C and methylsulfenyl chloride (3.1 g, 0.0375 mol) in benzene (5 ml) was added at this temperature. The reaction mixture was allowed to stand overnight. After the usual workup 2.8 g (61.5%) of (+)-**13**, $[\alpha]_{589}$ +21.0°, was obtained.

Treatment of (−)-**12**, $[\alpha]_{589}$ −5.5° (2.3 g, 0.017 mol), in benzene (30 ml) with triethylamine (2.56 g, 0.025 mol) and trimethylchlorosilane (2.7 g, 0.025 mol) at 0 °C gave after the usual workup (−)-*O*-isopropyl *O*-trimethylsilyl ethylphosphonite (**15**): $[\alpha]_{589}$ −14.4° (neat); bp 40–42 °C (3 mmHg); n^{20}D 1.4156 [very sensitive to moisture, contains small amounts of **12** (up to 5%)]; ^{1}H NMR (benzene) δ 4.1 (d sep, 1 H, $^3J_{CH_3-CH}$ = 6, $^3J_{CH-P}$ = 9.3 Hz), 1.2 (m, 11 H), 0.15 (s, 9 H).

Acknowledgment. We are indebted to Professor E. J. Goethals from the University of Ghent, Belgium, who kindly provided us with access to the 300-MHz NMR spectrometer. Miss J. Kmieć is thanked for skillful technical assistance with the experimental work.

Registry No.—*cis*-**1**, 7735-85-5; *trans*-**1**, 7735-81-i; *trans*-**3**, 50902-84-6; *cis*-**3**, 50902-83-5; *trans*-**4** DCHA, 35539-47-0; *cis*-**4** DCHA, 26284-89-9; *trans*-**5**, 23168-89-0; *cis*-**5**, 23168-88-9; *trans*-**6**, 60537-84-0; *cis*-**6**, 60537-85-1; *trans*-**7**, 60537-86-2; *cis*-**7**, 60537-87-3; *trans*-**8**, 60537-88-4; *cis*-**8**, 60537-89-5; *trans*-**9**, 53857-47-9; *cis*-**9**, 53909-41-4; *trans*-**10**, 60537-90-8; *cis*-**10**, 60537-91-9; *trans*-**11**, 40781-06-4; (+)-**12**, 31355-97-2; (−)-**12**, 60537-92-0; (−)-**13**, 60537-93-1; (+)-**13**, 60537-94-2; **14**, 60553-53-9; (−)-**15**, 60537-95-3; methyl iodide, 74-88-4; methylsulfenyl chloride, 5813-48-9; acetylsulfenyl chloride, 6405-82-9.

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(8) See, for example, R. Luckenbach, "Dynamic Stereochemistry of Pentacoordinated Phosphorus and Related Elements", Georg Thieme Verlag, Stuttgart, 1973.
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(14) M. Mikołajczyk and J. Łuczak, *Tetrahedron*, **28**, 5411 (1972).
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(17) M. I. Kabachnik and T. A. Mastriukova, *Zh. Obshch. Khim.*, **25**, 685, 1924 (1955); M. I. Kabachnik, T. A. Mastriukova, W. J. Kurotshin, and E. N. Popov, *ibid.*, **26**, 2228 (1956).
(18) G. Hilgetag and H. Teichmann, *Angew. Chem.*, **77**, 1001 (1965); J. Michalski, M. Mikołajczyk, and J. Omelańczuk, *Tetrahedron Lett.*, 3565 (1968).
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(21) E. A. Ishmaeva, M. Mikołajczyk, A. B. Remizov, and A. N. Pudovik, *Dokl. Akad. Nauk SSSR*, **223**, 351 (1975).
(22) L. D. Hall and R. B. Malcolm, *Chem. Ind. (London)*, 92 (1968).
(23) J. G. Verkade, "Interplay of Steric and Electronic Influences in the Chemistry of Monocyclic and Bicyclic Phosphorus Esters", the lecture given at the V International Conference on Organic Phosphorus Chemistry, Poland, Sept 1974; *Phosphorus*, in press; R. F. Hudson and J. G. Verkade, *Tetrahedron Lett.*, 3231 (1975); A. Okruszek and W. J. Stec, *Z. Naturforsch. B*, **30**, 430 (1975).
(24) It is interesting to note that in ^{1}H NMR spectra of *trans*-**3** and *cis*-**3** the relative chemical shifts of the axial and equatorial protons at C_5 are reversed. Whereas the equatorial proton in the solid isomer, *trans*-**3**, is upfield of 5a by 0.27 ppm, that in the liquid ester, *cis*-**3**, is downfield of 5a by 0.12 ppm. This may be due to different shielding effect exerted by the equatorial and axial phosphoryl group on the ring protons.
(25) Reaction of *cis*-**1** and *trans*-**1** with phenylsulfenyl chloride has been independently carried out by Denney and Moskal after our preliminary report: D. B. Denney and A. M. Moskal, *Phosphorus*, **4**, 77 (1974).
(26) M. Kainosho, T. Morofushi, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, **42**, 845 (1969); D. W. White, G. K. McEven, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1974).
(27) E. I. Nifantiev, J. W. Fursenko, and A. M. Sokurenko, *Zh. Obshch. Khim.*, **38**, 1909 (1968); A. A. Borisenko, N. M. Sergeev, E. I. Nifantiev, and Ju. A. Ustyniuk, *J. Chem. Soc., Chem. Commun.*, 408 (1972); E. I. Nifantiev, A. A. Borisenko, and N. M. Sergeev, *Dokl. Akad. Nauk SSSR*, **208**, 651 (1973).
(28) J. Michalski and A. Skowrońska, *J. Chem. Soc. C*, 703 (1970).
(29) See, for example, J. Michalski, A. Okruszek, and W. J. Stec, *Chem. Commun.*, 1495 (1970); M. Mikołajczyk and J. Łuczak, *Chem. Ind. (London)*, 701 (1974); J. Omelańczuk, P. Kiełbasiński, J. Michalski, J. Mikołajczak, M. Mikołajczyk, and A. Skowrońska, *Tetrahedron*, **31**, 2809 (1975).
(30) H. P. Benschop and G. R. Van den Berg, *Chem. Commun.*, 1431 (1970).
(31) The optical purity of thiol ester **13** was calculated on the basis of the properties of the optically pure ester **13** synthesized by Boter[32] having specific rotation $[\alpha]_D$ ±92.4°.
(32) H. L. Boter and D. H. J. M. Platenburg, *Recl. Trav. Chim. Pays-Bas*, **86**, 399 (1967); G. R. Van den Berg, D. H. J. Platenburg, and H. P. Benschop, *ibid.*, **91**, 929 (1972).
(33) T. L. Emmick and R. L. Letsinger, *J. Am. Chem. Soc.*, **90**, 3459 (1968).
(34) R. G. Van den Berg, D. H. J. M. Platenburg, and H. P. Benschop, *Chem. Commun.*, 606 (1971).

Reactions of Phosphorus Compounds. 37. Preparation of β-Iminopropyl- and β-Aminopropenyltriphenylphosphonium Bromides and the Use of the Latter in Heterocyclic Synthesis

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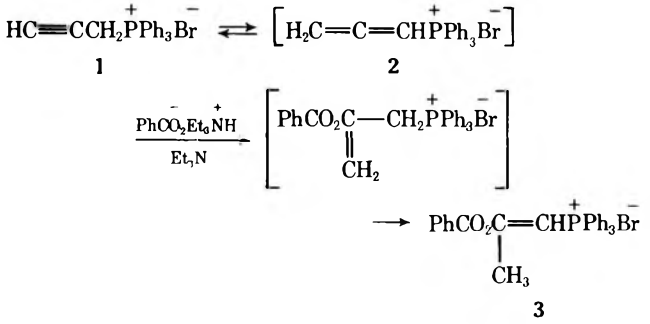
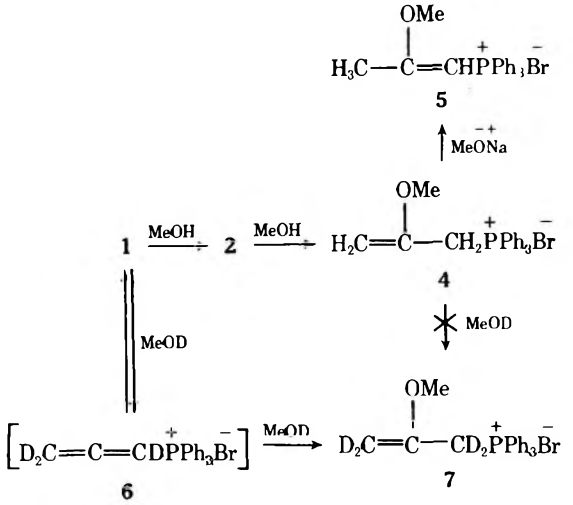
Support is given for the initial isomerization of prop-2-ynyltriphenylphosphonium bromide (1) to propadienyltriphenylphosphonium bromide (2) prior to the addition of nucleophiles to form substituted phosphonium salts. By ^{31}P NMR the 22 salts formed by the nucleophilic addition of primary amines to 2 were found to be in either the enamine or imine configuration. Synthesis of a number of substituted quinolines, 10, was accomplished by intramolecular Wittig reactions of the corresponding adducts, 8. Prop-1-ynyltriphenylphosphonium bromide was also prepared.

In 1965 Eiter and Oediger[1] reported the preparation of prop-2-ynyltriphenylphosphonium bromide (1) and its use in the Wittig reaction. The addition reactions of nucleophiles to prop-2-ynyl phenyl sulfones,[2] prop-2-ynyldialkylsulfonium salts,[3] and the corresponding sulfides[4] have been shown to be successful owing to an initial isomerization of the 2-alkynyl moiety to an allenyl species. Appleyard and Stirling only postulated[2] that the benzoate anion added to the allenyltriphenylphosphonium bromide (2) on going from 1 to the benzoate ester of 2-hydroxypropenyltriphenylphosphonium bromide (3). It has been shown conclusively in our laboratories



that 2 is the intermediate in conjugate additions of nucleophiles to 1.

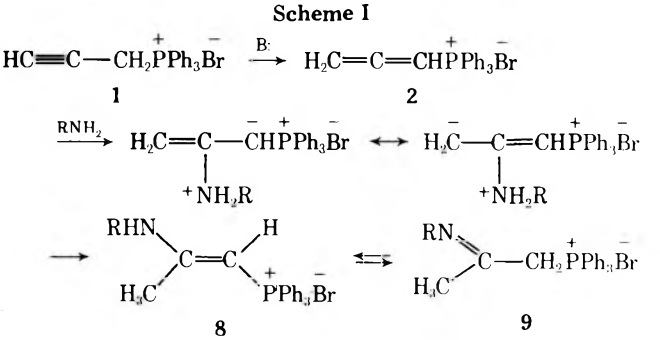
Methanol, as well as other alcohols, has been shown to add readily to 1, after an initiation period of approximately 2 h, under refluxing conditions, to give the 2-methoxyallyltriphenylphosphonium bromide (4). When a catalytic amount of base was added to the initial reaction mixture, or to a methanolic solution of 4, the 2-methoxypropenyltriphenylphosphonium bromide, 5, was formed rapidly. The reaction of deuteriomethanol with 1 gave 7. However, treatment of 4 with deuteriomethanol did not give 7, thus showing that the incorporation of deuterium into the molecule must have occurred during the conversion of 1 to the 1,3,3-trideuterioallenyltriphenylphosphonium bromide, 6, prior to the conjugate addition of methanol. The intermediacy of the allenyl salt, 2 (or 6), was thus shown.



Isolation of 2 was accomplished by treatment of 1 in *tert*-butyl alcohol with a catalytic amount of potassium *tert*-butylate.[5] The preparation of prop-1-ynyltriphenylphosphonium bromide was accomplished by heating 1 with phenol.

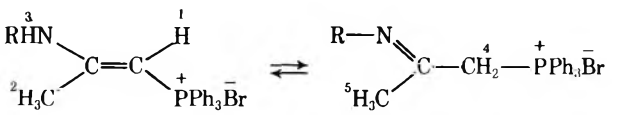
The mechanism of the nucleophilic addition of primary amines to the propargyl salt (1) is undoubtedly analogous to the addition of primary alcohols to 1 and is shown in Scheme I. We have added a large number of amines to salt 1. The yields

Scheme I

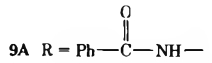
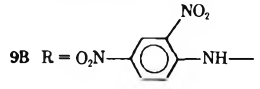
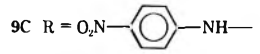
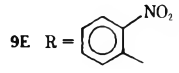
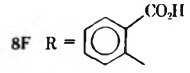
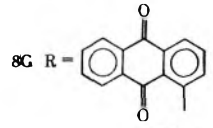
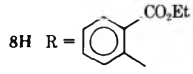
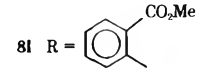
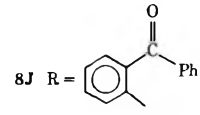
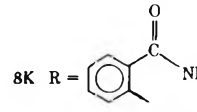
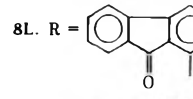
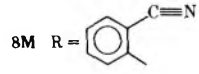
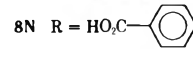
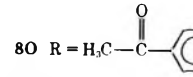
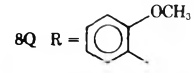
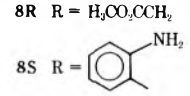
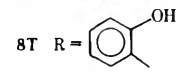
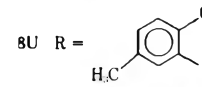
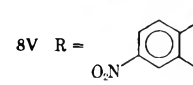


and physical data (^1H NMR, ^{31}P NMR, and IR spectra) for the phosphonium salts are given in Tables I, II, III, and IV, respectively. We have shown previously, by ^{13}C NMR,[6] that the stereochemistry about the carbon–carbon double bond in 8 was uniquely determined as the *E* form as shown. The ^1H NMR of the phosphonium salts showed either a methylene, for 9, at δ 4.80–5.65 ppm (d, 2, J_{PH} = 14.0–14.9 Hz) or a vinyl proton, for 8, at δ 3.75–5.10 ppm (d, 1, J_{PH} = 12.7–15.0 Hz) or, as in the case of 8E–9E, both, thus indicating the presence of an enamine–imine equilibrium. From the observed ^{31}P chemical shifts and the relative peak areas for each salt (A–V), we assigned the compound the structure 8 or 9 and calculated the percent composition ratio (8:9) as given in Table III. Further examination of the ^{31}P NMR data revealed two distinct ranges of chemical shifts (1) δ 12.9–18.6 ppm for the enamines or (2) δ 20.3–22.5 ppm for the imines, which is in agreement with our assignments of structure for the phosphonium salts 9A–8V. The assignment of the ^{31}P chemical shifts for the enamine or imine structure is supported by previous work[7,8] emanating from these laboratories.

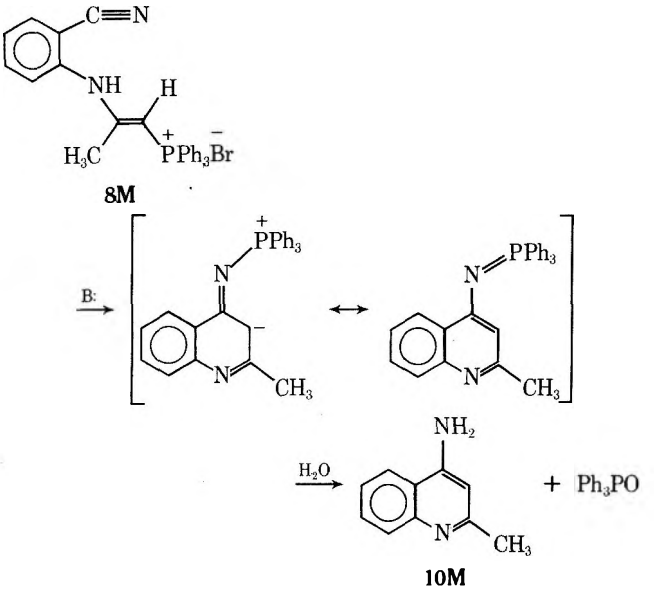
Table I



8 9

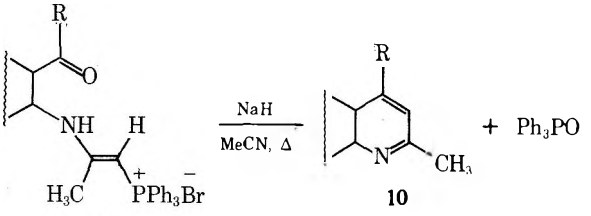
Salt	Mp, °C	% yield	Anal. Calcd C	Anal. Calcd H	Anal. Calcd N	Anal. Found C	Anal. Found H	Anal. Found N
9A R = 	259–260	86	65.00	5.06		64.78	4.98	
9B R = 	238	81	55.96	4.17		55.95	4.11	
9C R = 	233	81	60.68	4.71	7.86	60.46	4.57	7.33
9D R = Ph—NH—	208	60.5	66.26	5.35	5.72	66.71	5.63	5.42
9E R = 	207	92.5	62.44	4.66	5.39	62.35	4.79	5.39
8F R = 	221–222	70	64.87	4.86	2.70	64.72	4.91	2.63
8G R = 	206–207	10.9	69.54	4.50	2.31	69.35	4.74	2.19
8H R = 	159.5–160	74	65.94	5.34		65.75	5.20	
8I R = 	182–184	92	65.40	5.11		65.16	5.05	
8J R = 	220–221	95	70.58	5.04		70.41	5.28	
8K R = 	215–215.5	40	64.17	5.18		64.33	4.79	
8L R = 	231	81.6	70.84	4.72	2.43	70.65	5.25	2.35
8M R = 	245	60.5	67.34	4.84	5.61	67.45	4.86	5.36
8N R = 	281–282	78.2	64.87	4.86	2.70	64.37	4.68	2.53
8O R = 	218–219	40	67.45	5.27	2.71	67.39	5.24	2.43
8P R = Ph	262–263	88	66.35	5.31		68.34	5.50	
8Q R = 	212	94	66.67	5.39	2.78	66.68	5.42	2.53
8R R = $H_3CO_2CCH_2$	209	31	61.29	5.36	2.97	61.70	5.42	2.82
8S R = 	241–242	59	66.26	5.35	5.72	66.51	5.27	5.45
8T R = 	230–231	92	66.12	5.15	2.85	66.89	5.29	2.88
8U R = 	224	51	66.67	5.39	2.78	66.78	5.33	2.84
8V R = 	233–234	62	60.57	4.52	5.23	60.12	4.69	5.10

Synthesis of heterocyclic compounds via the Wittig reaction has been reviewed recently by Zbiral.[9] Our major interest in this work was the use of the phosphonium salts prepared above, substituted in such a manner to allow for an intramolecular Wittig reaction with a carbonyl (or nitrile) moiety, for the synthesis of heterocyclic species. We have previously shown[10] that upon treatment with base, several substituted salts, **8I** and **8J**, undergo an intramolecular Wittig reaction yielding substituted quinolines. We have further extended the application of this particular intramolecular Wittig reaction to include the synthesis of a simple quinoline (**10M**) by the



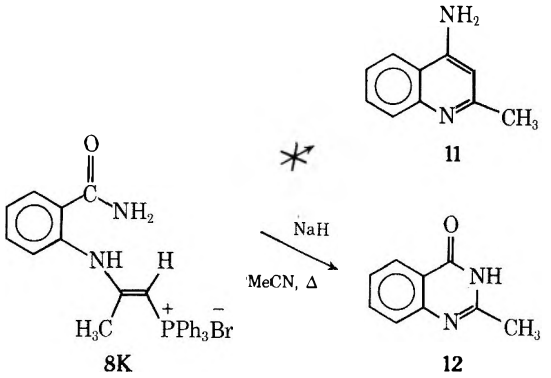
8M **10M**

attack of the ylide on a carbon–nitrogen triple bond[11] and the synthesis of tetracyclic quinolines (**10G**, **10L**). The physical (see Table V) and spectral data support the structures of the isolated products **10**.



8 **10**

Treatment of the esters **8H** and **8I** yields vinyl ethers, an abnormal pathway encountered previously.[12] Esters and ylides normally give β-ketophosphonium ylides;[13-15] therefore, one might anticipate that the amide, **8K**, would yield a vinyl



8K **11** **12**

amine, 2-methyl-4-aminoquinoline (**11**). However, 2-methylquinazol-4-one (**12**), was obtained via an unusual methylenephosphorane extrusion process.[16] An examination of the methylenephosphorane extrusion reaction is under investigation.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer, ^{1}H NMR spectra on a Perkin-Elmer Model R12B spectrometer using tetramethylsilane as internal standard, and ^{31}P NMR spectra on a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system. The ^{31}P NMR data were taken at the operating frequency of 36.43 MHz. The ^{31}P chemical shifts are reported as referenced to external 85% H_3PO_4 with shifts occurring downfield from the reference taken as positive. All melting points were uncorrected and obtained on a Thomas-Hoover capillary melting point apparatus. Elemental analyses are by Micro Analysis Inc., Wilmington, Del., and MHW Laboratories, Garden City, Mich. Any analytical and spectral data not included in text may be found in the tables. All reactions were run under dry nitrogen using anhydrous solvents.

Triphenyl(prop-2-ynyl)phosphonium Bromide (1).[1] To a solution of 210 g (0.80 mol) of triphenylphosphine and 400 ml of 1,4-dioxane in a 1-l. Morton flask fitted with a mechanical stirrer, reflux condenser, and dropping funnel, 90 ml of 48% HBr was added over a 30-min period. After the reaction mixture became homogeneous, 96 g (0.80 mol) of propargyl bromide was slowly added over a 90-min period. The reaction mixture was stirred for 3 h and filtered. Recrystallization with 2-propanol gave 230 g (75% yield) of **1** as white crystals: mp 179 °C dec (lit.[1] mp 156–158 °C); NMR (CF_3COOH) δ 2.3 (m, 1, J_{HH} = 2.8, J_{PH} = 6.5 Hz, C≡CH), 4.5 (dd, 2, J_{HH} = 2.8, J_{PH} = 15.0 Hz, -CH_2P); IR 1440, 1110 cm^{-1} (P-C).

Propadienyltriphenylphosphonium Bromide (2). A 3.8-g (0.01 mol) sample of **1** in 50 ml of dried Me_2SO was stirred with a catalytic amount of potassium *tert*-butylate for 2 h at room temperature under a nitrogen atmosphere. The deep red solution was precipitated by pouring it into 300 ml of ether. After two washings with ether, an orange solid, **2**, was obtained. The salt resisted recrystallization to give an analytical sample: IR ($CHCl_3$) 1960 (⟩C=C=C⟨), 1440 (C-P), 1115 cm^{-1} (P-phenyl), NMR ($CDCl_3$) δ 5.40 (dd, 2, J_{HH} = 6.5, J_{PH} = 13.0 Hz, H_2C=C=C⟨), 7.4–8.3 (m, 16, ⟩C=C=CHP and aromatic).

2-Methoxyprop-2-enyltriphenylphosphonium Bromide (4). To a 100-ml round-bottom flask equipped with a magnetic stirrer, reflux condenser, and nitrogen inlet 10.0 g (0.026 mol) of **1**, 40 ml of dry $CHCl_3$, and 20 ml (large excess) of freshly distilled methanol were added. The reaction mixture was heated at reflux with stirring for a period of 4 h. The yellow solution was then allowed to cool to room temperature and concentrated on a rotary evaporator to a yellow oil. Addition of EtOAc produced a solid which yielded 10.03 g (97% yield) of a white solid, **4**: mp 142 °C after recrystallization from $CHCl_3$–EtOAc; IR 1610 (C=C), 1420 (C-P), 1280 (C-O-C), 1100 cm^{-1} (P-phenyl); NMR)cdcl$_3$) δ 3.29 (s, 3, -OCH_3), 4.18 (dd, 1, J_{HH} = 2.5 ± 0.5 Hz, HC=C), 4.65 (dd, 1, J_{HH} = 2.5 ± 0.5 Hz, HC=C), 4.85 (d, 2, J_{PH} = 14 Hz, -CH_2P), 7.5–8.2 (m, 15, aromatic).

Anal. Calcd for $C_{22}H_{22}OPBr$: C, 63.78; H, 5.60. Found: C, 63.85; H, 5.69.

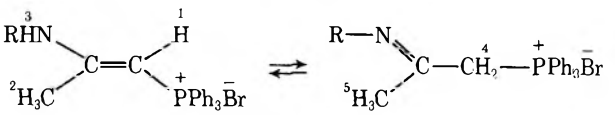
2-Methoxyprop-1-enyltriphenylphosphonium Bromide (5). To a 50-ml round-bottom flask equipped with a magnetic stirrer, reflux condenser, and nitrogen inlet, 20 ml (large excess) of freshly distilled CH_3OH and a catalytic amount of sodium were added. After hydrogen evolution ceased, 3.80 g (0.01 mol) of **1** was added and the solution was heated at reflux for 10 min. The solution was then concentrated to an oil on a rotary evaporator and the oil poured slowly into 200 ml of EtOAc with stirring. A solid, **5**, separated which upon crystallization had mp 155 °C and weighed 3.73 g (90% yield): IR 1601 (C=C), 1420 (C-P), 1330 (C-O-C), 1110 cm^{-1} (P-phenyl); NMR δ 2.60 (s, 3, -CH_3), 3.68 (s, 3, -OCH_3), 5.68 (d, 1, J_{PH} = 17 Hz, =CHP), 7.4–8.0 (m, 15, aromatic).

Anal. Calcd for $C_{22}H_{22}OPBr$: C, 63.78; H, 5.60. Found: C, 63.89; H, 5.36.

2-Methoxy-1,1,3,3-tetradeuterioprop-2-enyltriphenylphosphonium Bromide (7). The salt **7** was prepared in the same manner as **4** above. Freshly distilled CH_3OD was substituted for the CH_3OH. The melting point and IR were essentially identical with those of **5**. The NMR ($CDCl_3$) showed δ 3.30 (s, 3, -OCH_3), 7.5–8.2 (m, 15, aromatic).

Prop-1-ynyltriphenylphosphonium Bromide. To a 100-ml flask equipped with a magnetic stirrer, reflux condenser, and nitrogen inlet were added 10 g (0.026 mol) of **1**, 60 ml of CH_2Cl_2, and 2.50 g (equimolar amount) of phenol. The mixture was heated at reflux with stirring until all of the solid was dissolved. The solution was allowed to cool and the stirring was continued for 3 h. The mixture was then

Table II. ^{1}H NMR (δ)



8 9

Salt	1	2	3	4	5	Aromatic	Other
9A				5.40 (d, 2, J_{PH} = 14.6 Hz)	2.20 (s, 3)	7.4–8.3 (m, 21)	CH_2 (d, 2, J = 13.4 Hz) 4.6 CH_3 (s, 3) 1.8 OH in aromatic region[a]
9B				5.40 (d, 2, J_{PH} = 14.5 Hz)	2.20 (s, 3)	7.5–8.1 (m, 18)	NH (d, 1, J = 2.66 Hz) 8.8
9C				5.30 (d, 2, J_{PH} = 14.9 Hz)	2.20 (s, 3)	7.5–8.2 (m, 19)	NH (s, 1) 10.3
9D				4.80 (d, 2, J_{PH} = 14.0 Hz)	2.15 (s, 3)	6.5–8.0 (m, 20)	NH (s, 1) 8.87
9E	4.25 (d, 1, J_{PH} = 13.3 Hz)	2.30 (s, 3)	10.6 (bs, 1)	5.65 (d, 2, J_{PH} = 12.0 Hz)	2.3 (d, 3, J = 2.6 Hz)	7.5–8.3 (m, 19)	
8F	4.4 (d, 1, J_{PH} = 14.7 Hz)	1.85 (s, 3)	10.1 (bs, 1)			7.1–8.2 (m, 19)	
8G	5.03 (d, 1, J_{PH} = 13.4 Hz)	2.03 (s, 3)	10.6 (bs, 1)			7.0–7.8 (m, 22)	
8H	4.55 (d, 1, J_{PH} = 14.3 Hz)	2.0 (s, 3)	10.3 bs, 1)			7.0–8.2 (m, 19)	CH_2 (q, 2, J = 7.0 Hz) 4.3 CH_3 (t, 3, J = 7.0 Hz) 1.3
8I	4.5 (d, 1, J_{PH} = 14.74 Hz)	2.05 (s, 3)				6.95–8.3 (m, 19)	$-\overset{O}{\overset{\|}{C}}OCH_3$ (s, 3) 3.85
8J	4.20 (d, 1, J_{PH} = 15.0 Hz)	1.75 (s, 3)				7.2–8.2 (m, 24)	
8K	4.40 (d, 1, J_{PH} = 14.5 Hz)	1.80 (s, 3)	10.13 (bs, 1)			7.4–8.2 (m, 19)	NH_2 (s, 2) 8.5
8L	4.50 (d, 1, J_{PH} = 13.4 Hz)	2.00 (s, 3)	10.2 (bs, 1)			7.1–7.9 (m, 22)	
8M	4.15 (d, 1, J_{PH} = 13.5 Hz)	2.00 (s, 3)	10.7 (bs, 1)			7.3–7.9 (m, 19)	
8N	5.10 (d, 1, J_{PH} = 14.9 Hz)	1.85 (s, 3)	10.15 (bs, 1)			7.5–8.1 (m, 19)	OH in aromatic region
8O	5.08 (d, 1, J_{PH} = 14.9 Hz)	1.95 (s, 3)	10.3 (bs, 1)			7.5–8.1 (m, 19)	$-\overset{O}{\overset{\|}{C}}-CH_3$ (s, 3) 2.55
8P	4.75 (d, 1, J_{PH} = 15.0 Hz)	2.05 (s, 3)	10.50 (bs, 1)			7.2–7.8 (m, 20)	
8Q	4.15 (d, 1, J_{PH} = 14.7 Hz)	2.00 (s, 3)	9.8 (bs, 1)			6.9–7.7 (m, 19)	$-OCH_3$ (s, 3) 3.8
8R	3.75 (d, 1, J_{PH} = 12.7 Hz)	1.90 (s, 3)	9.0 (bs, 1)			7.5–7.9 (m, 15)	CH_2 (d, 2, J_{PH} = 6.0 Hz) 4.2 OCH_3 (s, 3) 3.73
8S	3.95 (d, 1, J_{PH} = 14.7 Hz)	1.85 (s, 3)	9.5 (bs, 1)			6.5–8.0 (m, 19)	NH_2 (s, 2) 5.4
8T	4.15 (d, 1, J_{PH} = 14.7 Hz)	1.85 (s, 3)	9.5 (bs, 1)			6.75–8.0 (m, 20)	OH in aromatic region
8U	4.10 (d, 1, J_{PH} = 15.3 Hz)	1.80 (s, 3)	9.6 (bs, 1)			6.9–8.0 (m, 19)	CH_3 (s, 3) 2.2
8V	4.30 (d, 1, J_{PH} = 13.3 Hz)	1.85 (s, 3)	10.0 (bs, 1)			7.25–8.35 (m, 19)	OH in aromatic region

[a] See footnote *a*, Table III.

poured slowly with stirring into 200 ml of EtOAc. Stirring was continued until a white solid was produced. The solid was twice recrystallized from $CHCl_3$–EtOAc to give 8.5 g (85% yield) of prop-1-ynyltriphenylphosphonium bromide as white crystals. The salt appears to exist in two crystalline forms, one having mp 130 °C and the second mp 193 °C. Both forms give the same NMR and IR spectra. IR ($CHCl_3$) 2900 (C–H), 2200 (C≡C), 1440 (C–P), 1110 cm^{-1} (P–phenyl); NMR ($CDCl_3$) δ 2.75 (d, 3, J_{PH} = 5 Hz, $-CH_3$), 7.5–8.2 (m, 15, aromatic).

Anal. Calcd for $C_{21}H_{18}PBr$: C, 66.30; H, 4.76. Found: C, 66.35; H, 4.72.

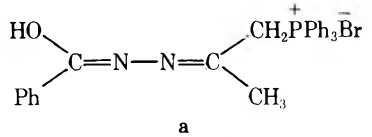
General Procedure for the Preparation of the β-Aminopropenyltriphenylphosphonium Bromides (9A–8V). Into a dry flask, fitted with a reflux condenser, gas inlet, and magnetic stirrer, were placed equimolar amounts (0.02 mol) of the amine, triphenyl(prop-2-ynyl)phosphonium bromide (1), and 200 ml of CH_3CN (dried and distilled over P_2O_5). The mixture was stirred and refluxed until TLC indicated the disappearance of the phosphonium salt, 1 (3 h to 3 days). After cooling, the mixture was concentrated to an oil, dissolved in a minimum amount of CH_2Cl_2, and added slowly with stirring to EtOAc. The solution was stirred for 0.5 h and then filtered. The product was recrystallized to a constant melting point in CH_2Cl_2–EtOAc. The results are shown in Table I.

General Procedure for the Preparation of Substituted Quinolines (10). Equimolar amounts of the phosphonium salt (9 or 8) and NaH (57% in mineral oil) were allowed to react in a 500-ml one-neck round-bottomed flask fitted with a reflux condenser and nitrogen inlet by dissolving the salt in dry CH_3CN and then adding the NaH which was washed three times with hexane. More CH_3CN was added so that the total volume was 250 ml. The reaction mixture was refluxed and stirred under nitrogen for 3 days. After cooling, the mixture was filtered and poured into water. The water layer was extracted three times with ether, made basic with KOH, and extracted two more times with ether. The combined ether layers were dried (K_2CO_3), filtered, and concentrated to an oil (crude product 10) with a rotary evaporator. The workup is described below.

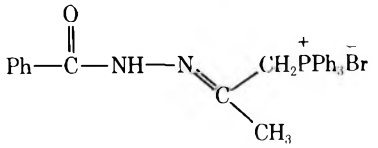
Table III. ^{31}P NMR (δ)

Salt	%8:%9	δ 8, ppm	δ 9, ppm
9A	0:100[a]		(19.1) 20.2
9B	0:100		21.0
9C	0:100		21.1
9D	0:100		21.8
9E	1:2	16.3	21.2
8F	6:1	15.6	22.2
8G	5:1	15.6	22.0
8H	5:1	16.7	22.5
8I	3:1	16.4	22.0
8J	3:1	12.9	20.3
8K	>99:trace	15.9	21.8
8L	>99:trace	16.1	21.6
8M	>99:trace	16.4	21.3
8N	>99:trace	15.4	21.5
8O	100:0	16.8	
8P	100:0	16.8	
8Q	100:0	16.4	
8R	100:0	16.0	
8S	100:0	15.5	
8T	100:0	15.3	
8U	100:0	15.4	
8V	100:0	18.6	

[a] 9A has structures a and b in a 1:1 ratio. [b] The chemical



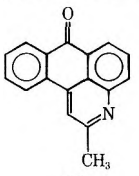
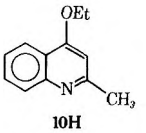
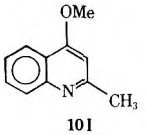
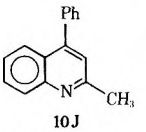
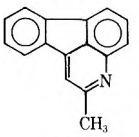
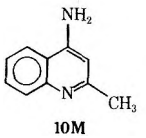
a



b

shifts are referenced to external 85% H_3PO_4 with shifts occurring downfield from the reference taken as positive. All samples were run at 28 °C with broad band ^{1}H decoupling.

Table V. Quinoline Derivatives

	Mp, °C	% yield	m/e Theory	m/e Exptl
 10G	190	41.2	245.0840	245.0840
 10H	48	59.5	187.0997	187.0956
 10I	63–65	53		
 10J	96.5–98	64	219.1048	219.1034
 10L	135	42	217.0891	217.0906
 10M	167–169	31		

2-Methyldibenz[*f,i,j*]isoquinol-7-one (10G). The oil obtained from treating compound **8G** by the general procedure was placed on a silica gel column and eluted with EtOAc to remove unreacted starting material. The resulting oil was dissolved in 95% EtOH and added to an equal volume of picric acid in 95% EtOH (saturated). The yellow crystals, picrate derivative of **10G**, were collected and recrystallized in 95% EtOH. The picrate salt was then dissolved in a minimal amount of EtOH, placed on an alumina column, and eluted with petroleum ether. Concentration of the fractions yields the desired product **10G**: mp 190 °C; NMR ($CDCl_3$) δ 2.9 (s, 3, $-CH_3$), 7.3–8.8 (m, 8, aromatic).

4-Ethoxy-2-methylquinoline (10H). The oil obtained from treating compound **8H** by the general procedure was purified in the

Table IV. Major Infrared Absorption Bands (cm^{-1})

Salt	P–Ph	P–C	N–H	Olefin	>C=N	>C=O	Other
9A	1100		2900		1600		
9B	1100	1430	3200		1650		1525 d, 1430 d
9C	1105	1440	2900, 3100		1600		1490
9D	1100	1440	3000		1590		
9E	1110	1440	3000		1580		1540
8F	1100	1440	3200	1600		1725	1260
8G	1090	1420	3000	1525		1680	1260, 1310
8H	1110	1440	3000	1530		1720	1240, 1290
8I	1110	1430	3400	1650		1700	1290
8J	1110	1440				1750	
8K	1110	1420	3000–3600	1560		1680	
8L	1110	1440	3050	1600		1700	
8M	1110	1430	3000	1580			2250
8N	1085					1680	
8O	1090	1440	2900	1550		1660	
8P	1110	1440					1220
8Q	1100	1410	2900	1550			1260
8R	1100	1440	3100, 3300	1550		1780	1200
8S	1090	1440	3300	1550			1590, 990
8T	1100	1420	3300	1500			3200
8U	1110	1430	3200	1500			1580
8V	1100	1420	3400	1490			1575

same manner as **10G** above to yield the desired product **10H**: mp 48 °C; NMR ($CDCl_3$) δ 1.5 (t, 3, J_{HH} = 11.3 Hz, $-CH_2CH_3$), 2.6 (s, 3, $-CH_3$), 4.15 (q, 2, J_{HH} = 11.3 Hz, $-CH_2CH_3$), 6.5 (s, 1, 3-aromatic proton), 7.2–8.3 (m, 4, aromatic).

2-Methyl-4-methoxyquinoline (10I). The oil obtained from treating compound **8I** by the general procedure was sublimed three times to give colorless crystals, 0.23 g (30% yield) of **10I**. A 53% yield of Ph_3PO, mp 150–153 °C, was found; **10I** had mp 63–65 °C (lit.[17] mp 58–59 °C).

2-Methyl-4-phenylquinoline (10J). The oil obtained from treating compound **8J** by the general procedure was sublimed at 80 °C under vacuum. The material left after sublimation was impure Ph_3PO in 90% yield. The sublimate weighed 0.55 g (64% yield), slightly yellow needles, **10J**, mp 96.5–98 °C (lit.[18] mp 97–98 °C).

2-Methylindeno[1,2,3-*de*]quinoline (10L). The oil obtained from treating compound **8L** by the general procedure was purified in the same manner as **10G** to yield the desired product **10L**: mp 135 °C dec; NMR ($CDCl_3$) δ 2.8 (s, 3, $-CH_3$), 7.2–8.0 (m, 8, aromatic).

4-Amino-2-methylquinoline (10M). The oil obtained from treating compound **8M** by the general procedure was dissolved in CH_2Cl_2 and dripped slowly into hexane. The resulting precipitate was collected and recrystallized in benzene–hexane to yield 0.29 g (31% yield) of **10M**, mp 167–169 °C (lit.[19] mp 167–169 °C).

Registry No.—**1**, 2091-46-5; **2**, 54599-99-4; **4**, 60661-63-4; **5**, 60661-64-5; **7**, 60661-65-6; **8F**, 60661-66-7; **8G**, 60661-67-8; **8H**, 60661-68-9; **8I**, 60661-69-0; **8J**, 60661-70-3; **8K**, 60661-71-4; **8L**, 60661-72-5; **8M**, 60661-73-6; **8N**, 60661-74-7; **8O**, 60661-75-8; **8P**, 54774-75-3; **8Q**, 60661-76-9; **8R**, 54774-76-4; **8S**, 60661-77-0; **8T**, 60661-78-1; **8U**, 60661-79-2; **8V**, 60661-80-5; **9A** (keto form), 60661-81-6; **9B**, 60661-82-7; **9C**, 60661-83-8; **9D**, 54774-78-6; **9E**, 60661-84-9; **10G**, 60661-85-0; **10H**, 46272-56-4; **10I**, 31835-53-7; **10J**, 1721-92-2; **10L**, 60661-86-1; **10M**, 6628-04-2; triphenylphosphine, 603-35-0; propargyl bromide, 106-96-7; methanol, 67-56-1; CH_3OD. 1455-13-6; prop-1-ynyltriphenylphosphonium bromide, 54599-98-3; benzoic acid hydrazide, 613-94-5; 2,4-dinitrophenylhydrazine, 119-26-6; 4-nitrophinylhydrazine, 100-16-3; phenylhydrazine, 100-63-0; 2-nitrobenzenamine, 88-74-4; 2-aminobenzoic acid, 118-92-3; 1-amino-9,10-anthracenedione, 82-45-1; ethyl 2-aminobenzoate, 87-25-2; methyl 2-aminobenzoate, 134-20-3; (2-aminophenyl)phenylmethanone, 2835-77-0; 2-aminobenzamide, 88-68-6; 1-amino-9*H*-fluoren-9-one, 6344-62-3; 2-aminobenzonitrile, 1885-29-6; 4-aminobenzoic acid, 150-13-0; 1-(4-aminophenyl)ethanone, 99-92-3; benzenamine, 62-53-3; 2-methoxybenzenamine, 90-04-0; methyl glycinate, 616-34-2; 1,2-benzenediamine, 95-54-5; 2-aminophenol, 95-55-6; 2-amino-4-methylphenol, 95-84-1; 2-amino-4-nitrophenol, 99-57-0; triphenylphosphine oxide, 791-28-6; **9A** (enol form), 61484-35-3.

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The Effect of the Base Strength upon the Structure of the Transition State in E2 Reactions. Kinetics of Eliminations from 2-Arylethyltrimethylammonium Bromides Promoted by Sodium Phenoxide and Sodium *m*-Nitrophenoxide in *N,N*-Dimethylformamide

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Values of the Hammett constant, ρ, and deuterium kinetic isotope effect (k_H/k_D) have been determined for the eliminations from 2-arylethyltrimethylammonium bromides promoted by sodium phenoxide and sodium *m*-nitrophenoxide in *N,N*-dimethylformamide. These values indicate that the transition state of the reaction with sodium phenoxide has a carbanion character higher than that of the reaction with sodium *m*-nitrophenoxide. The phenomenon is mainly due to a significant decrease of C_α–leaving group bond stretching at the transition state of the reaction with the stronger base since the degree of C_β–H bond rupture in the reaction with sodium phenoxide is smaller than in the reaction with sodium *m*-nitrophenoxide. These results are compared with those obtained in the elimination from 2-arylethyl bromides and discussed in the light of recent theories concerning the effect of structural changes in the reactants on the transition state of E2 reactions.

The study of the effect of structural changes in the reactants on the structure of the transition state of E2 reactions is of great importance from both theoretical and practical points of view. Recently, on the basis of theoretical treatments, it has been shown that both parallel and perpendicular modes of vibration of the transition state can be affected by structural changes in the reactants.[1,2] The effects on the parallel modes (parallel effects) result in modifications of the structure of the transition state in agreement with the Hammond postulate;[3] those on the perpendicular modes (perpendicular effects) result in modifications in the opposite direction. As a further development of the theory, it has been also suggested that the relative weight of perpendicular and parallel effects can closely depend on the location of the transition state in the reaction

Table I. Kinetic Data for the Elimination Reactions of p-Y-$C_6H_4CZ_2CH_2N^+(CH_3)_3Br^-$ with Phenoxides in DMF at 55.7 °C

Registry no.	Y	Z	Sodium phenoxide[a]	Sodium m-nitrophenoxide
6068-85-5	H	H	$1.23 \pm 0.01 \times 10^{-3}$	$4.15 \pm 0.02 \times 10^{-5}$
1012-70-0	H	D	$4.35 \pm 0.15 \times 10^{-4}$ [b]	$1.85 \pm 0.11 \times 10^{-5}$ [b]
19836-63-6	CH_3	H	$3.26 \pm 0.02 \times 10^{-4}$	$1.31 \pm 0.01 \times 10^{-5}$
6948-08-9	OCH_3	H	$6.95 \pm 0.38 \times 10^{-5}$	$2.94 \pm 0.16 \times 10^{-6}$
60582-50-5	Br	H	$1.12 \pm 0.08 \times 10^{-2}$	$2.90 \pm 0.03 \times 10^{-4}$

[a] In the presence of $NaClO_4$ (0.46 N). [b] Corrected for the presence of the undeuterated compound.

Table II. Hammett Correlations and Kinetic Isotope Effects in Elimination Reactions of 2-Arylethyltrimethylammonium Bromides Promoted by Phenoxides in DMF at 55.7 °C

Nucleophile	ρ	k_H/k_D
Sodium phenoxide	4.25[a]	2.83 ± 0.12
Sodium m-nitrophenoxide	3.81[b]	2.26 ± 0.14

[a] $r = 0.994$; $S = 0.125$. [b] $r = 0.991$; $S = 0.137$.

potential energy diagram.[4-6a] An important consequence appears to be that systems with an E1cB-like or an E1-like transition state are expected to display a sensitivity to variations in the structure of reactants significantly different from that of systems characterized by a "central" transition state. In this way it has been possible to rationalize some apparent discrepancies concerning leaving group effects and substituent effects at C_β in elimination reactions involving transition states with different degrees of carbanion character.

Recently, we have clearly shown that in the eliminations from 2-arylethyl bromides promoted by phenoxides in *N,N*-dimethylformamide (DMF) a change to a stronger base leads to a more carbanionic transition state.[7] This result is in agreement with theoretical predictions[2,6a] since the reaction should take place by way of a transition state in the central-E1cB region where perpendicular and parallel effects are expected to be of comparable importance. However, according to the theory a completely different result (less carbanion character with the stronger base) should be expected for a reaction utilizing an E1cB-like transition state, a clear predominance of parallel effects being predicted in this case.[6] With the aim of obtaining information on this point we have investigated the effect of base strength on the elimination reactions of 2-arylethyltrimethylammonium salts.

Results and Discussion

Kinetics of the reactions of para-substituted 2-phenylethyltrimethylammonium bromides (substituents: Br, H, CH_3, OCH_3) and 2-phenylethyl-2,2-d_2-trimethylammonium bromide with sodium phenoxide and sodium *m*-nitrophenoxide have been carried out in DMF at 55.7 °C by spectrophotometric analysis of styrene or para-substituted styrene. Aliquots of the reaction mixture were withdrawn, the olefin extracted by *n*-heptane, and the optical density of the solution measured after appropriate dilution. The spectrophotometric yield in olefin was larger than 95% in each case.

The concentration of substrate was ca. 2×10^{-3} M; that of nucleophile, 0.03–0.06 M with sodium phenoxide and 0.36 M with sodium *m*-nitrophenoxide. In the experiments with sodium phenoxide, $NaClO_4$ (0.46 M) was also present in order to keep constant the salt concentration during the reaction. Good first-order plots were obtained and, in the presence of $NaClO_4$, the second-order rate constant was independent of the phenoxide concentration.

The kinetic results, collected in Table I, satisfactorily correlate with the Hammett equation. The ρ values (reported in Table II together with the values of the deuterium kinetic isotope effect, k_H/k_D) are among the more positive ever recorded for an E2 reaction[8] (even larger that the ρ values reported for the eliminations from the same substrates promoted by EtONa and *t*-BuOK in the corresponding alcohols[9]) and clearly indicate a transition state of high carbanion character for both eliminations. Likewise, also the very low k_H/k_D values observed are in agreement with an activated complex in which the transfer of the proton to the base is almost complete.

The comparison between the ρ values shows that the reaction with sodium phenoxide ($pK_a \simeq 18$)[10] has a transition state with a higher carbanion character than that of the reaction with sodium *m*-nitrophenoxide ($pK_a = 15.4$);[10] it follows that, also in eliminations characterized by an E1cB-like transition state, a change to a stronger base produces a significant increase in the carbanion character of the transition state. This result parallels that observed in the reaction of 2-phenylethyl bromides where the ρ value was found to rise from 1.84 to 2.64 for a ca. 4×10^5-fold increase in the nucleophile basicity.[7] As in the reactions of bromo derivatives,[7,11] the result obtained in eliminations from ammonium salts is due mainly to a decreased degree of C_α–leaving group bond breaking in the transition state of the reaction with the stronger base and not to an increase in the extent of C_β–H bond breaking. In fact, since the proton transfer is well past the midpoint, the larger k_H/k_D value found with sodium phenoxide indicates a smaller degree of rupture of this bond as the base strength increases.

In conclusion, a change of the nucleophile basicity has an effect on the transition state structure of E2 reactions which does not seem to depend upon the character of the transition state in a substantial way. A more "reactant-like" transition state appears to be the general outcome for reactions occurring by way of either a central or E1cB-like transition state. Since this result is caused, to a large extent, by a decrease of C_α–leaving group bond stretching at the transition state, an increase in the carbanion character is also observed.

However, when the effect on the degree of C_β–H bond breaking is considered, E1cB-like and central transition states appear to display a different sensitivity to changes in nucleophile basicity. Accordingly, in going to a stronger base the extent of C_β–H bond breaking decreases in the reaction of 2-arylethyltrimethylammonium ions, whereas it remains practically unchanged in the reaction of 2-arylethyl bromides.[10] The result for the E1cB-like transition state is in agreement with the Hammond postulate (less proton transfer with the stronger base) and therefore supports the suggestion[5] that parallel effects can be somewhat more important than the perpendicular ones in E1cB-like transition states, even if this is not sufficient to produce a less carbanionic transition state as the nucleophile basicity is increased.

The effects caused by changes in the intrinsic basicity of the nucleophile on the transition state structure of E2 reactions can also be compared with those caused by changes in the medium basicity (brought about by modifications in base association and/or solvation), even though in this latter case

the interpretation of the data can often be made uncertain by the concomitant change in the nature of the solvent. Interestingly, results similar to those of the present work have been obtained in the eliminations from 2-arylethyldimethylsulfonium bromides promoted by NaOH in H_2O–Me_2SO,[12,13] where an increase in the Me_2SO concentration was found to determine a rise in the ρ value and a concomitant decrease in the extent of C–H and C–S bond breaking in the transition state. Likewise, a more carbanionic transition state was observed in the syn-elimination reactions of 2-arylcyclopentyl tosylates as the base–solvent system was changed from *t*-BuOK–*t*-BuOH to crown ether complexed *t*-BuOK in *t*-BuOH.[14] It does not seem possible, however, to generalize these results since in the reactions of 2-arylethyl bromides the structure of the transition state appears not be affected to a significant extent by modifications in the medium basicity.[15,16] A similar situation also obtains in the elimination from 1-arylethyltrimethylammonium salts promoted by ethoxide ions in EtOH–Me_2SO mixture.[17]

Finally we wish to note the fact that the ρ value for the eliminations from 2-arylethyltrimethylammonium salts decreases as the base–solvent system is changed from EtONa–EtOH to *t*-BuOK–*t*-BuOH.[9] In the light of present results it does not seem possible to attribute this decrease to a base-strength effect.

However, when the base–solvent system is changed from EtONa–EtOH to *i*-PrOK–*i*-PrOH an increase in the ρ value is observed for the eliminations from both 2-arylethyltrimethylammonium salts and the corresponding sulfonium salts.[18] For the latter compounds the increase is very large and has been attributed to a decrease in C_α–S bond breaking in the more basic medium greater than the decrease in C_β–H bond rupture.

Experimental Section

Materials. 2-Arylethyltrimethylammonium bromides were prepared by reaction in methanol of the corresponding 2-arylethyl bromides[15] with an aqueous solution (33%) of trimethylamine. The mixture was allowed to stand at room temperature until separation of the solid product, which was recrystallized from ethanol–ether. Their properties were as follows.

2-Phenylethyltrimethylammonium bromide, mp 238–239 °C (lit.[9] 238–239 °C).

2-Phenylethyl-2,2-d_2-trimethylammonium bromide, mp 238.5–239 °C (lit.[9] 238–239 °C). Mass spectra showed 86% of deuteration.

2-(*p*-Tolyl)ethyltrimethylammonium bromide, mp 198–199 °C (lit.[9] 200.5–201 °C).

2-(*p*-Anisyl)ethyltrimethylammonium bromide, mp 216.5–218 °C (lit.[9] 217.7–218.2 °C).

2-(*p*-Bromophenyl)ethyltrimethylammonium bromide, mp 258.5–259.5 °C.

Sodium phenoxide was prepared by reaction of phenol with equimolecular amounts of NaOH in water. Water was removed at reduced pressure and the residue recrystallized from dry acetone. Before use, the phenoxide was kept at 100 °C and 1 mm for 90 min.

Sodium *m*-nitrophenoxide was prepared from *m*-nitrophenol and sodium methoxide in methanol. Methanol was removed at reduced pressure, and the residue recrystallized from ethanol–benzene and dried for 3 h at 100 °C and 1 mm.

Sodium perchlorate was a commercial product (B.D.H.), used without further purification.

Kinetic Studies. Known amounts of quaternary ammonium salt, of the nucleophile, and, in the case of the reaction with sodium phenoxide, of $NaClO_4$ were placed into a volumetric flask (20 ml). DMF (a commercial product, Carlo Erba RPE) was added and, after dissolution of all materials, the solution was diluted to the calibration mark. After shaking, the flask was placed in a thermostated bath and allowed to come to thermal equilibrium. Aliquots (2 ml) were taken periodically and poured into a separatory funnel containing *n*-heptane (8 ml), water (50 ml), and 6 N HNO_3 (1 ml). After rapid mixing the organic layer was separated and the aqueous phase further extracted with *n*-heptane (2 × 7 ml). The combined organic layers were washed twice with water and diluted to 25 ml in a volumetric flask. The optical density of the resulting solution was determined at the following wavelengths (nm): 249, styrene; 252, *p*-methylstyrene; 258, *p*-methoxystyrene; and 255, *p*-bromostyrene. Blank experiments have shown complete recovery of the olefin with this procedure.

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Registry No.—Sodium phenoxide, 139-02-6; sodium *m*-nitrophenoxide, 3019-85-0.

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Preparation of 6-(Bromomethyl)-2,4-pteridinediamine Hydrobromide and Its Use in Improved Syntheses of Methotrexate and Related Compounds

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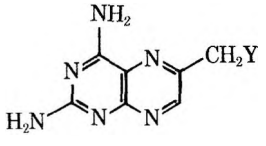
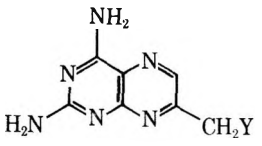
A versatile method for the introduction of the (2,4-diamino-6-pteridinyl)methyl grouping which involves the reaction of 6-(bromomethyl)-2,4-pteridinediamine hydrobromide (**3**) with nucleophiles is demonstrated by facile syntheses of methotrexate (**4b**), aminopterin (**4c**), and the corresponding 4-amino-4-deoxypteroic acids **4d** and **4e** in good yields and high states of purity. 2,4-Diamino-6-pteridinemethanol (**1a**), the precursor of 3, prepared by condensation of 2,4,5,6-tetraaminopyrimidine with 1,3-dihydroxyacetone and partially purified as its hydrobromide, typically contained approximately 5% 6-methyl-2,4-pteridinediamine (**1b**) and less than 1% each of 2,4-diamino-7-pteridinemethanol (**2a**) and 7-methyl-2,4-pteridinediamine (**2b**). The coproduct **1b** persisted in 3, which was prepared from **1a** HBr by treatment with dibromotriphenylphosphorane, but the final products (4 series) were shown by reversed-phase, high-pressure liquid chromatography to be free of **1b**.

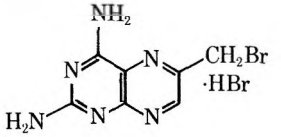
The use of massive doses of methotrexate (**4b**) followed by leucovorin rescue in the clinical treatment of certain neoplasms[1] has made desirable the accessibility of **4b** in a higher state of purity than that previously available[2] and has also greatly increased supply demands. A new process that shows promise of meeting these needs makes use of 6-(bromomethyl)-2,4-pteridinediamine hydrobromide (**3**), a versatile intermediate prepared initially for use in an improved approach to analogues of **4b** and aminopterin (**4c**) bearing varied side chains.[3] We wish to amplify on the preliminary reports of the synthesis of **3** and present results illustrating its use in syntheses of **4b**, **4c**, the corresponding 4-amino-4-deoxypteroic acids **4d** and **4e**, and pteroic acid (**5**).



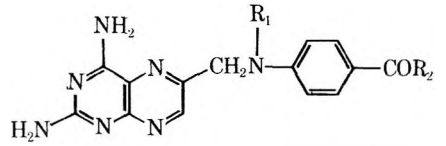
1a, Y = OH
b, Y = H



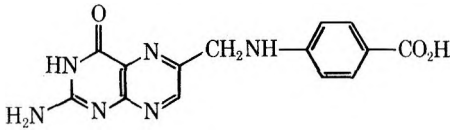
2a, Y = OH
b, Y = H



3



4a, R_1 = Me; R_2 = $NHCH(CO_2Et)(CH_2)_2CO_2Et$
b, R_1 = Me; R_2 = $NHCH(CO_2H)(CH_2)_2CO_2H$
c, R_1 = H; R_2 = $NHCH(CO_2H)(CH_2)_2CO_2H$
d, R_1 = Me; R_2 = OH
e, R_1 = H; R_2 = OH



5

2,4-Diamino-6-pteridinemethanol (**1a**), the precursor of **3**, was prepared by the condensation of 2,4,5,6-tetraaminopyrimidine with 1,3-dihydroxyacetone in aqueous sodium acetate solution as described by Baugh and Shaw.[4] Possible coproducts were discussed in the work cited, and limited evidence that only **1a** is isolated was presented. We found through ^1H NMR spectral studies on the crude material filtered directly from the reaction mixture that **1a** is the major product, but 6-methyl-2,4-pteridinediamine (**1b**) is also detectable.[3] Analysis by reversed-phase, high-pressure liquid chromatography (HPLC) further revealed minor contamination by 2,4-diamino-7-pteridinemethanol (**2a**) and 7-methyl-2,4-pteridinediamine (**2b**).[5,6] Partial purification of **1a** was effected through its hydrobromide, which crystallized from a solution of the crude product mixture in ethanol containing hydrobromic acid. A typical run afforded a product whose ^1H NMR spectrum indicated a molar ratio of **1a** to **1b** of 16–20:1, and analysis by HPLC revealed about 5% of **1b** and less than 1% each of **2a** and **2b**. No further purification of **1a** was required, since contaminants present at this point are ultimately removed without attentive effort. The level of each is diminished in subsequent conversions, and reversed-phase HPLC analyses that aided in establishing the end products to be of high purity and free of **1b** are discussed later.

The bromomethyl function of **3** was introduced by treatment of **1a** HBr with dibromotriphenylphosphorane (Ph_3PBr_2) in *N,N*-dimethylacetamide (Me_2NAc).[7] Involvement of the amino groups, possibly through direct reaction with Ph_3PBr_2 to form an aminophosphonium salt,[8] was indicated by a required minimum ratio of Ph_3PBr_2 to **1a** HBr of 3:1. In early preparative runs, a 4:1 ratio was used, but later use of a 3.3:1 ratio gave similar results. After the excess reagent had been decomposed, the Me_2NAc was removed by evaporation in vacuo, or the product was caused to precipitate by the addition of benzene to the reaction solution. The crude initial product was then dissolved in hot acetic acid. If the amino groups were substituted, regeneration was effected during this treatment. Crystalline **3**, solvated by acetic acid, separated from the solution. Even though the coproduct **1b** persisted, the **3** thus obtained proved to be of suitable purity for many synthetic applications. Further recrystallization of **3** did not remove **1b**, but was apparently beneficial in some applications (for example, in the preparation of **4c**). The amount of **1b** still present in **3** was estimable from ^1H NMR spectral data. In deuteriotrifluoroacetic acid, **3** produces singlet peaks at δ 4.70 (CH_2) and 9.08 (C_7 H), and peaks due to **1b** occur at δ 2.83 (CH_3) and 8.85 (C_7 H). Results from numerous runs showed **1b** present in **3** at levels slightly lower than in the precursor **1a**.

Treatment of **1a** HBr with the complex formed by phosphorus tribromide and *N,N*-dimethylformamide was also found to give **3**, but the best yield of suitable product obtained from three runs was a relatively poor 11%. This possible alternative method was not pursued because it appeared un-

likely that it could be made superior to that using Ph_3PBr_2 in Me_2NAc, which gave **3** in about 50% yield after recrystallization.

In earlier related work, deaza analogues of **4e** were prepared by sequences involving side-chain bromination of methyl-substituted precursors (N^2,N^4-dibenzoylated deaza analogues of **1b**),[9] but attempts to extend that method to the pteridine series led to the finding that bromination of the N^2,N^4-diacetyl derivative of **1b**, even with equimolar amounts of bromine or *N*-bromosuccinimide, afforded only the dibromomethyl derivative.[10]

Reaction of **3** with aromatic amines in Me_2NAc to give the **4** series did not require inclusion of an auxiliary base. In the initial preparation of **4c**, 3 molar equiv of *N*-(4-aminobenzoyl)-L-glutamic acid was used, but later use of 2 equiv did not affect the yield. Three equivalents of 4-aminobenzoic acid was used in the preparation of **4e** HBr, which crystallized from the reaction medium. The methylamino compounds were alkylated by **3** at a slower rate than the primary amines under the same conditions. This difference might be attributable to a less favorable equilibrium between free amine and protonated form in the absence of an auxiliary base. Reaction of **3** with the methylamino compounds at 25 °C required several days to reach completion, but conversion was complete within 5 h at 55 °C, even when the methylamino compounds were present in only slight excess. Unchanged methylamino precursors were troublesome to remove from the products when large excesses were used, but only 10% excess proved adequate.

The immediate precursor of **4b**, diethyl ester **4a**, could be hydrolyzed in situ or, preferably, isolated beforehand. The ester crystallized as a partial hydrobromide after the reaction solution had been combined with water. The overall yield of **4b** of high purity obtained from the isolated ester was 73% whereas that of product of comparable purity obtained after hydrolysis in situ was 58%.

Previously reported syntheses of pure **4d**[11-13] are quite lengthy and tedious compared with the present approach. Used in conjunction with carboxyl-activating reagents, **4d** has served as a key intermediate in syntheses of **4b**[13] and analogues of **4b** in which the glutamic acid portion is replaced by amino acid esters or amines.[12b] Oligo-γ-L-glutamyl peptide analogues of **4b** have been prepared from **4d** (derived from **4b** by enzymic cleavage) by an adaptation of the Merrifield method.[14,15]

This simply executed method wherein **3** is used to attach the (2,4-diamino-6-pteridinyl)methyl grouping to diverse side chains also affords access to corresponding (2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl compounds. Thus, alkaline hydrolysis of the labile 4-amino group of **4e** gave pteroic acid (**5**),[16] which has been used in syntheses of pteroyloligo-γ-L-glutamates,[17,18] pteroyl-γ-L-glutamyl peptides bearing various amino acids,[19] and simpler folic acid analogues derived from various amino acids.[20] Earlier sources of **5** involve lengthy synthetic routes[21] or enzymic cleavage of folic acid.[17,22]

Reversed-phase HPLC analyses (discussed in the Experimental Section) showed the products prepared from **3** to be of high purity, and no special purification efforts were required. Previously reported methods either give crude products whose purification requires laborious techniques of limited capacity[23,24] or involve lengthy routes that afford relatively poor yields.[11-13,21]

Despite reports that show the enantiomeric purity of **4b** to be of importance with respect to biologic or anticancer activity,[23b,25] no specific rotation for **4b** has been reported. Optical activity is retained in both **4b** and **4c** prepared directly from **3**. Treatment of the mixed anhydride derived from **4d** and isobutyl chloroformate with diethyl L-glutamate gave the ester **4a** identical with that prepared from **3** and the intact side-chain ester. The **4b** obtained by hydrolysis of **4a** prepared in this manner gave a specific rotation value in acceptable agreement with that of **4b** prepared from **3** and the intact side chain. These findings indicate that racemization is not involved in the formation of products from **3** and the intact side chains bearing glutamic acid residues.

Experimental Section

High-pressure liquid chromatographic studies were made with a Waters Associates ALC-242 liquid chromatograph equipped with a UV detector (254 nm) and an M-6000 pump using a μBondapak C_{18} column of 30 cm length and 4 mm inside diameter. Thin layer chromatographic analyses were performed on products whose side chains bear carboxyl groups on DEAE–cellulose sheets (Bakerflex) using 0.5 M NaCl, 0.2 M in mercaptoethanol, in 0.005 M KH_2PO_4 buffer solution at pH 7.0. Samples were dissolved for spotting in 0.01 N NaOH. Chromatograms were viewed by three UV lamps (Models UVL-21, UVS-12, and C-51; Ultraviolet Products, Inc.), and each compound appeared homogeneous. Most of the elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Spectral determinations, specific rotation measurements, and some of the elemental analyses were performed in the Molecular Spectroscopy Section of Southern Research Institute under the direction of Dr. W. C. Coburn, Jr. The ^1H NMR spectra were determined with a Varian XL-100-15 spectrometer (except those for **2a** and **4e**, which were determined on a Varian T-60A) in the solvent indicated using Me_4Si as internal reference. Chemical shifts (δ in ppm) listed for multiplets were measured from the approximate centers, and relative integrals of peak areas agreed with those expected for the assignments indicated. Addition of D_2O produced the expected simplifications in the spectra. The UV spectra were determined with a Cary Model 17 spectrometer. Samples were first dissolved in appropriate media (**1a** HBr and **4a**, MeOH or EtOH; **3**, 2-PrOH; **4b–e** and **5**, 0.01 N NaOH), and the solutions were diluted tenfold with the medium given in the listings. Maxima are expressed in nanometers with the molar absorbance ($\epsilon \times 10^{-3}$) given in parentheses. Molecular weights used in all calculations conform with the compositions listed with elemental analysis results. Specific rotations were measured with a Rudolph Model 80 polarimeter; concentration (*c*) is given in grams of solute per 100 ml of 0.1 N NaOH. Products were dried in vacuo (<1 mm) at room temperature over P_2O_5 unless other conditions are specified.

2,4-Pteridinediamine-6-methanol (1a) Hydrobromide. Dried and pulverized crude **1a** [47 g, prepared as reported[4] from 2,4,5,6-tetraaminopyrimidine (0.293 mol) but not recrystallized] was stirred with EtOH (6 l.) at 70–75 °C, and a solution of 48% HBr (28 ml) in EtOH (500 ml) was added in a thin stream. The mixture was refluxed for about 5 min with rapid stirring while nearly all of the solid dissolved. The solution was clarified (Norit, Celite) while hot, and the clear yellow filtrate was kept in a refrigerator overnight while a first crop (17.2 g) separated. A second crop (10.2 g) was obtained after concentration of the filtrate (to 2 l.) by evaporation under reduced pressure. The two crops were combined before examination by HPLC and determination of spectral properties, yield 34% (based on tetraaminopyrimidine). Spectral data: UV, 0.1 N HCl, 243 nm (15.4), 284 (5.06), 337 (9.60), 350 (sh); 0.1 N NaOH, 225 nm (11.6), 257 (21.3), 368 (6.97); ^1H NMR (CF_3CO_2D) δ 5.27 (s, CH_2), 9.08 (s, C_7 H), and weak singlets due to **1b** at δ 2.84 and 8.85; estimated molar ratio of **1a** to **1b**, 20:1.

Anal. Calcd for $C_7H_8N_6O$·HBr: C, 30.79; H, 3.32; N, 30.77. Found: C, 31.19; H, 3.33; N, 31.39.

6-(Bromomethyl)-2,4-pteridinediamine Hydrobromide (3). Method A. Br_2 (59.6 g, 0.373 mol) was added dropwise during 30 min to a stirred (Teflon paddle) solution of Ph_3P (97.7 g, 0.373 mol) in Me_2NAc (500 ml) kept near 10 °C. A smooth suspension containing crystalline solid resulted. Solid **1a** HBr (25.4 g, 93.0 mmol) was then added in one portion. The cooling bath was removed, and after 1 h at 20–25 °C, solution occurred. The solution, which developed a dark red color, was kept at 20–25 °C for 1 h longer and was then chilled (ice bath) and treated with EtOH (6 ml). After overnight refrigeration, the solvent was removed by evaporation in vacuo (<1 mm, bath to 45 °C). The dark semisolid residue was stirred with two 300-ml portions of C_6H_6, and each portion was removed from the C_6H_6-insoluble product by decantation. The solid that remained was stirred with glacial AcOH (660 ml) preheated to 80 °C. The mixture was kept in a bath at 80 °C until solution was complete. Beige, crystalline solid separated when the solution was allowed to cool. The mixture was left overnight in a refrigerator before the solid was collected, washed with

AcOH (cooled to 10 °C) followed by Et_2O, and dried in vacuo (over P_2O_5 and NaOH pellets) at successive temperatures of 25, 56, and 110 °C to give yellow **3** in 49% yield (15.3 g). Spectral data: UV, 0.1 N HCl, 249 nm (17.3), 339 (10.5), 353 (sh); 0.1 N NaOH, 258 nm (21.5), 370 (6.94); ^{1}H NMR (CF_3CO_2D) δ 4.70 (s, CH_2), 9.08 (s, C_7 H) and a weak singlet at δ 2.83 due to the Me group of **1b**; molar ratio of **3** to **1b**, ~25:1.

Anal. Calcd for $C_7H_7BrN_6$·HBr: C, 25.02; H, 2.40; N, 25.01. Found: C, 25.59; H, 2.79; N, 24.62.

A twice-recrystallized (from AcOH) sample (dried as before) from another run gave elemental analysis results that agreed closely with values calculated for **3** although its ^{1}H NMR spectrum indicated the molar ratio of **3** to **1b** to be ~20:1 (~96% purity by weight).

Anal. Calcd for $C_7H_7BrN_6$·HBr: C, 25.02; H, 2.40; Br, 47.56; N, 25.01. Found: C, 25.22; H, 2.44; Br, 47.30; N, 24.99.

Method B. Solid **1a** HBr (300 g, 1.10 mol)[26] was added to a mixture of Ph_3PBr_2 (3.63 mol) and Me_2NAc (3.6 l.) prepared as described under method A in a 20-l., three-necked flask. The mixture was stirred at 20–25 °C for 3.5 h. The solution that formed was treated dropwise during 15 min with EtOH (72 ml) and stirred for 15 min longer before C_6H_6 (11.7 l.) was added. A dark oil precipitated, and the mixture was stirred for 30 min longer and left to stand overnight. The clear supernatant was siphoned and decanted from the now semisolid precipitate, which was dissovled with stirring in hot glacial AcOH (6 l., preheated to 100 °C). The solution was filtered while hot, and the beige, crystalline material that separated from the cooled filtrate was collected after 4 h at 20–25 °C. The Et_2O-washed solid (290 g of **3** solvated by AcOH) was recrystallized from 2-PrOH to give lustrous yellow-orange platelets, which were washed with Et_2O before being pulverized and dried, yield 209 g (two crops of 168 and 41 g). Typical lots of **3** prepared in this manner were found through ^{1}H NMR spectral data (in CF_3CO_2D) to be solvated to slightly varying degrees by 2-PrOH, usually near hemisolvates. (The percentage yield of **3** $0.5C_3H_7OH$ from the above run was 52%; six runs on similar scales gave an average yield of 45%.) One exception was a lot found to be a monosolvate: ^{1}H NMR (CF_3CO_2D) δ 1.3–1.5 (m, 6, Me from 2-PrOH and 2-PrOCOCF$_3$), 4.70 (s, 2, CH_2Br), 9.08 (s, 1, C_7 H); molar ratio of **3** to **1b**, ~40:1. Elemental analysis results given below support the indicated composition for this lot; UV, 0.1 N HCl, 249 nm (18.7), 339 (11.1), 353 (sh); 0.1 N NaOH, 258 nm (23.2), 370 (7.61).

Anal. Calcd for $C_7H_7BrN_6$·HBr·C_3H_7OH: C, 30.32; H, 4.07; Br, 40.35; N, 21.22. Found: C, 30.50; H, 3.92; Br, 39.97; N, 21.28.

Diethyl *N*-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamate (4a). A. Directly from 3. A mixture of **3** C_3H_7OH (1.98 g, 5.00 mmol) and diethyl *N*-[4-(methylamino)benzoyl]-L-glutamate[27] (1.85 g, 5.50 mmol) in Me_2NAc (20 ml) was stirred at 50–55 °C (bath temperature) for 4 h (solution occurred after 2 h), left at 25 °C for 17 h, and combined with H_2O (200 ml). A clear solution resulted, but yellow solid began separating after a few minutes. After a refrigeration period (4 h), the solid was collected, washed with H_2O, and dried. The orange solid (2.12 g) underwent a weight increase and became yellow on exposure to ambient conditions of the laboratory; yield 77% (2.22 g). Spectral data: UV, 0.1 N HCl, 243 nm (18.9), 306 (24.0); pH 7, 258 nm (25.6), 306 (26.5), 372 (8.49); 0.1 N NaOH, 258 nm (26.2), 303 (25.6), 372 (8.18); ^{1}H NMR (Me_2SO-d_6) δ 1.2 (m, CH_3CH_2), 2.1 (m, $CHCH_2CH_2$), 2.4 (m, CH_2CO_2Et), 3.24 (s, MeN), 4.1 (m, CH_2Me), 4.4 (m, $NHCHCO_2Et$), 4.85 (s, CH_2N), 6.85 and 7.76 (two d, C_6H_4), 7.40 (br s, NH_2), 8.3 (d, CONH, over broad s, NH_2), 8.68 (s, C_7 H).

Anal. Calcd for $C_{24}H_{30}N_8O_5$·0.5HBr·1.5H_2O: C, 49.86; H, 5.93; Br, 6.91; N, 19.39. Found: C, 49.48; H, 6.04; Br, 7.07; N, 19.43.

Most of **4a** 0.5HBr·1.5H_2O described above was used for conversion to **4b**. A sample (200 mg) was stirred with a mixture of $CHCl_3$ and 0.3 N NH_4OH (60 ml of each). After 10 min, the $CHCl_3$ layer was removed, washed three times with H_2O, dried (Na_2SO_4), and evaporated. The yellow solid residue was recrystallized from MeCN to give **4a** (150 mg) with melting point, mixture melting point, TLC, and spectra (IR, UV, and ^{1}H NMR) identical with those of **4a** prepared from **4d** as described below.

B. From 4d. A stirred mixture of pulverized **4d** 1.5H_2O (1.06 g, 3.00 mmol), Et_3N (606 mg, 6.00 mmol), and *N*,*N*-dimethylformamide–Me_2SO (60 ml, 1:1) was treated at 0–5 °C with a solution of isobutyl chloroformate (615 mg, 4.50 mmol) in dioxane (1 ml). The mixture was stirred at 0–5 °C for 15 min before diethyl L-glutamate HCl (1.44 g, 6.00 mmol) was added followed by more Et_3N (606 mg). The mixture was stirred for 15 min longer at 0–5 °C and then for 30 min at 25–30 °C. The insoluble material, mostly Et_3N·HCl, was removed by filtration, and the filtrate was concentrated to ~10 ml by evaporation in vacuo (<1 mm, bath 25–30 °C). Addition of H_2O (80 ml) gave an orange solid. After refrigeration, the solid was collected and then stirred for 10 min with a mixture of $CHCl_3$ (100 ml) and 0.3 N NH_4OH (50 ml). The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to give a yellow solid, which was recrystallized from MeCN to give **4a**, mp 155–157 °C, in 10% yield (160 mg); homogeneous by TLC.[12a,28] Spectral data: UV, in agreement with that given above for **4a** 0.5HBr·1.5H_2O; ^{1}H NMR (Me_2SO-d_6) δ 1.2 (m, CH_3CH_2), 2.1 (m, $CHCH_2CH_2$), 2.4 (m, CH_2CO_2Et), 3.22 (s, MeN), 4.1 (m, CH_2Me), 4.4 (m, $NHCHCO_2Et$), 4.80 (s, CH_2N), 6.60 (s, NH_2), 6.85 and 7.76 (two d, C_6H_4), 7.54 (br s, NH_2), 8.3 (d, CONH), 8.60 (s, C_7 H).

Anal. Calcd for $C_{24}H_{30}N_8O_5$·0.5H_2O: C, 55.48; H, 6.01; N, 21.57. Found: C, 55.56; H, 6.05; N, 21.63.

***N*-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic Acid (4b, Methotrexate). A. From Isolated 4a.** The ester **4a** 0.5HBr·1.5H_2O (1.80 g, 3.12 mmol) was dissolved in warm EtOH (50 ml), and the solution was cooled to 20 °C and treated with 1 N NaOH (10 ml). The sodium salt of **4b** began separating from the stirred solution after about 2 h at 20–25 °C. After 24 h, H_2O (40 ml) was added to dissolve the yellow solid, and the solution was evaporated under reduced pressure (H_2O aspirator, bath at 20–25 °C) until the EtOH had been removed. The clear aqueous solution (~30 ml) was diluted with H_2O (to 60 ml) and treated with 1 N HCl to lower the pH to 7.0. The solution was filtered to ensure clarity before the pH was finally lowered to 4.0 to cause precipitation of **4b**. After overnight refrigeration, the yellow-orange solid was collected, washed with H_2O followed by Et_2O, and dried. The solid was pulverized, dried further, and then allowed to equilibrate with ambient conditions of the laboratory, yield 95% (1.50 g), $[\alpha]^{24}D$ +19.0 ± 0.1° in 0.1 N NaOH (c 1.1). Spectral data: UV, in agreement with that reported;[23a] ^{1}H NMR, identical with that listed below under B.

Anal. Calcd for $C_{20}H_{22}N_8O_5$·3H_2O: C, 47.24; H, 5.55; N, 22.04. Found: C, 47.43; H, 4.91; N, 22.18.

B. Without Isolation of 4a. A mixture of **3** (3.0 g of ~95% purity, 8.5 mmol; molar ratio **3** to **1b**, 15:1) and diethyl *N*-[4-(methylamino)-benzoyl]-L-glutamate[27] (3.3 g, 9.8 mmol) in Me_2NAc (36 ml) was stirred at 20–25 °C under N_2 in a stoppered flask protected from light. Solution occurred within 24 h. After 120 h, H_2O (180 ml) was added with rapid stirring followed immediately by 2 N NaOH (18 ml). More H_2O (90 ml) was added within 5 min. Nearly all of the semisolid precipitate that formed when the NaOH was added dissolved within 10 min. The solution phase was decanted into another flask, and the small amount of semisolid that remained was dissolved in Me_2NAc (10 ml). This solution was treated with 2 N NaOH (2 ml) and combined with the main portion. The basic solution was kept under N_2 in a stoppered flask protected from light for 20 h and then treated with 1 N HCl to lower the pH (from 10.5) to 5.5. The solution was treated with Norit and filtered through a mat of compressed cellulose powder (~1 cm thick in a 150-ml Buchner funnel). The mat was washed with H_2O until the wash solution was colorless. Acidification to pH 4.0 caused precipitation of **4b** as a voluminous yellow-orange solid. The mixture was stirred with ice-bath cooling for 2 h before the product was collected, then redissolved by suspending it in H_2O (300 ml) and treating the stirred suspension with 2 N NaOH (9 ml). The isolation process (acidification to pH 5.5, treatment with Norit, filtration through cellulose mat, acidification to pH 4.0, and stirring at 0–5 °C for 2 h) was repeated. The collected product was washed with H_2O, dried, and allowed to equilibrate with ambient conditions of the laboratory, yield 58% (2.49 g), $[\alpha]^{21}D$ +18.7 ± 0.5° in 0.1 N NaOH (c 1.0). Spectral data: ^{1}H NMR (Me_2SO-d_6) δ 2.0 (m, $CHCH_2CH_2$), 2.3 (m, CH_2CO_2H), 3.22 (s, Me), 4.4 (m, $NHCHCO_2H$), 4.82 (s, CH_2N), 6.85 and 7.73 (two d, C_6H_4), 7.00 (s, NH_2), 7.9 (br s, NH_2), 8.2 (d, NHCO), 8.62 (s, C_7 H).

Anal. Found: C, 47.36; H, 5.04; N, 22.22 (see calcd given above).

The same results were obtained when the alkylation step was carried out at 53–57 °C for 4 h.

C. From 4a Prepared from 4d. Hydrolysis of **4a** (derived from **4d**) as described under A above led to **4b**, $[\alpha]^{24}D$ +17.5 ± 0.7° in 0.1 N NaOH (c 0.99), in 90% yield. The spectral (UV and ^{1}H NMR) and chromatographic (TLC and HPLC) properties of this sample were identical with those of **4b** described above.

***N*-[4-[(2,4-Diamino-6-pteridinyl)methyl]benzoyl]-L-glutamic Acid (4c, Aminopterin).** A mixture of **3** (53.8 g prepared by method B, 0.147 mol as **3** $0.5C_3H_7OH$) and *N*-(4-aminobenzoyl)-L-glutamic acid (84.0 g, 0.316 mol) in Me_2NAc (630 ml) was stirred at 25 °C under N_2 in a stoppered flask protected from light for 18 h. The solution that formed was poured slowly into H_2O (4.5 l.) at 80 °C with stirring. The resulting solution was allowed to cool and kept for 6 h at 20–25 °C while yellow **4c** deposited in granular form. The mixture was then left in a refrigerator for 16 h. The collected solid was washed successively with H_2O, EtOH, Me_2CO, and Et_2O, yield 72% (49.4 g), $[\alpha]^{24}D$ +17.5 ± 0.3° in 0.1 N NaOH (c 1.1). Spectral data: UV, in

agreement with that reported;[23a] ^{1}H NMR (Me_2SO-d_6) δ 2.0 (m, $CHCH_2CH_2$), 2.3 (m, CH_2CO_2H), 4.4 (m, $NHCHCO_2H$), 4.54 (s, CH_2N), 6.85 and 7.72 (two d, C_6H_4), 6.8 (CH_2NH under part of the C_6H_4 multiplet), 7.0 (broad s, NH_2), 8.2 (d, NHCO plus NH_2), 8.76 (s, C_7 H).

Anal. Calcd for $C_{19}H_{20}N_8O_5 \cdot 1.6H_2O$: C, 48.63; H, 4.98; N, 23.88. Found: C, 48.87; H, 4.86; N, 23.87.

4-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino]benzoic Acid (4d). A solution of **3** (171 mg of ~97% purity, 0.49 mmol; molar ratio of **3** to **1b**, 25:1) and 4-(methylamino)benzoic acid (83 mg, 0.55 mmol) in Me_2NAc (2 ml) was stirred at 25 °C for 114 h and then mixed with H_2O (18 ml). The solid that separated (150 mg) was dissolved in NaOH solution (7.5 ml of 0.08 N), and treatment of the clarified (Norit, Celite) solution with dilute HCl to produce pH 6.5 gave yellow **4d**, yield 60% (105 mg) (dried in vacuo at 78 °C over P_2O_5). Spectral data (UV, IR, and ^{1}H NMR) agreed with that reported earlier.[11]

Anal. Calcd for $C_{15}H_{15}N_7O_2 \cdot 1.5H_2O$: C, 51.13; H, 5.15; N, 27.83. Found: C, 51.02; H, 5.24; N, 27.52.

In a larger run, a mixture of **3** (12.0 g of ~96% purity, 34.3 mmol; molar ratio of **3** to **1b**, 19:1) and 4-(methylamino)benzoic acid (5.93 g, 39.3 mmol) in Me_2NAc (140 ml) was stirred at 55 °C (bath temperature) for 4 h. Pure **4c** $1.5H_2O$ was isolated as before in 61% yield (7.40 g), UV, IR, and ^{1}H NMR spectra identical with those of the sample described above.

Anal. Found: C, 50.88; H, 4.86; N, 27.82 (see calcd given above).

4-[[(2,4-Diamino-6-pteridinyl)methyl]amino]benzoic Acid (4e) Hydrobromide (1:1). A mixture of 4-aminobenzoic acid (2.06 g, 15.0 mmol) and pulverized **3** C_3H_7OH (1.98 g, 5.00 mmol) in Me_2NAc (25 ml) was stirred at 25 °C for 24 h. The yellow solid was collected with the aid of Me_2NAc and washed with H_2O followed by Et_2O, yield 94% (1.83 g). Spectral data: UV, 0.1 N HCl, 242 nm (16.5), 297 (22.0), 334 (plateau) (11.6); pH 7, 260 nm (28.7), 278 (sh), 370 (7.81); 0.1 N NaOH, 260 nm (28.9), 278 (sh), 370 (7.71). A suitable solvent was not found for determination of the ^{1}H NMR spectrum of **4e** HBr. A sample was dissolved in dilute NaOH, and treatment with AcOH led to **4e**, whose spectrum was determined in Me_2SO-d_6. The sample was, however, solvated by AcOH as evidenced by a singlet at δ 2.0 (CH_3). The remainder of the spectrum was as follows: δ 4.5 (s, CH_2), 6.8 and 7.6 (two d, C_6H_4, overlapping NH and NH_2), 8.8 (s, C_7 H).

Anal. Calcd for $C_{11}H_{13}N_7O_2 \cdot HBr$: C, 42.87; H, 3.60; Br, 20.37; N, 25.00. Found: C, 42.74; H, 4.08; Br, 20.39; N, 24.80.

4-[[(2-Amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoic Acid (5, Pteroic Acid).[16] A stirred mixture of **4e** HBr (6.60 g, 16.8 mmol) and 0.2 N NaOH (1.2 l.) was refluxed under N_2 for 1.5 h. The cooled and filtered (Norit, Celite) solution was treated with 3 N HCl to lower the pH to 3.5, and the yellow precipitate that formed was collected by centrifugation, suspended in H_2O (1 l.), and redissolved by addition of the required amount of 1 N NaOH. The precipitation process described above was repeated, and **5** was first collected by centrifugation, then suspended in H_2O and collected by filtration, yield 70% (3.66 g). Spectral data (^{1}H NMR and UV) agreed with reported results.[21b,22]

Anal. Calcd for $C_{14}H_{12}N_6O_3$: C, 53.84; H, 3.87; N, 26.91. Found: C, 53.64; H, 3.83; N, 26.83.

HPLC Analyses. Compounds **4b** and **4c** were examined by reversed-phase HPLC using four mobile phases: A, 0.1 M Tris buffer (pH 6.7)–MeOH (4:1); B, 0.1 M KH_2PO_4 (pH 6.7)–MeOH (83:17); C, 0.005 M NH_4OAc (pH 5)–MeCN (85:15); D, H_2O–MeCN (3:2). This sensitive technique revealed only very minor impurities in each of these products. The absence of **1b** from both was confirmed by analyses using mobile phases A and D. Deliberate mixtures of **1b** with **4b** or **4c** were well resolved using these phases, and peak area ratios were still measurable using phase A in prepared mixtures containing as little as 0.5% of **1b**. Total organic impurities in **4b** prepared as described amounted to well below 1%. None of the impurities commonly seen in the **4b** in clinical use prior to development of this process was detected using phase C, which was used by Tong and co-workers in developing a HPLC assay method for **4b**.[2] The total impurities present in the **4b** used in the Tong study amounted to 5.9%; the main contaminants were N^{10}-methylfolic acid (2.7%) and **4d** (1.6%). The total organic impurity level in **4c** prepared as described was somewhat greater than in **4b**, usually amounting to approximately 1%. Mixtures of folic acid, **4c**, and **4b** elute, in the order given, with baseline separation using mobile phase A.[5] There was no indication of folic acid in **4c**. Two minor contaminants were detected, one of which was identified as *N*-(4-aminobenzoyl)-L-glutamic acid. Results on **4e**, **5** (phase A), and **4d** (phase C) also indicated only very minor amounts of impurities.

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Registry No.—**1a**, 945-24-4; **1a** HBr, 57963-59-4; **1b** HBr, 60662-06-8; **3**, 52853-40-4; **4a**, 43170-88-3; **4a** 0.5HBr, 60662-07-9; **4b**, 59-05-2; **4b** Na, 15475-56-6; **4c**, 54-62-6; **4d**, 19741-14-1; **4e** HBr, 60662-08-0; **5**, 119-24-4; diethyl *N*-[4-(methylamino)benzoyl]-L-glutamate, 2378-95-2; diethyl L-glutamate HCl, 1118-89-4; *N*-(4-aminobenzoyl)-L-glutamic acid, 4271-30-1; 4-(methylamino)benzoic acid, 10541-83-0; 4-aminobenzoic acid, 150-13-0.

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(6) Authentic samples of **1b** and **2b** were prepared by the instructions given in ref **23a**. Condensation of glyceraldehyde with 2,4,5,6-tetraaminopyrimidine using the conditions for the related reaction with 1,3-dihydroxyacetone[4] gave **2a** of suitable purity for use as a marker in the HPLC studies.[5] The UV spectral data from **2a** thus prepared agreed with that reported,[10] and the structural assignment is supported by ^{1}H NMR spectral data: δ (in Me_2SO-d_6) 4.6 (s, CH_2), 6.6 (br s, NH_2), 7.6 (br s, NH_2), 8.4 (s, C_6 H); δ (in CF_3CO_2D) 5.3 (s, CH_2), 9.0 (s, C_6 H). The chemical shifts (in CF_3CO_2D) for C_7 H of **1a** and C_6 H of **2a** were resolved in a deliberate mixture of the two, but those due to the CH_2 groups were not.
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Reduction of Organic Halides with Zn–Cu to Deuterated Compounds and a Convenient Carbon-13 Magnetic Resonance Method of Deuterium Analysis

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A preparation of a Zn–Cu couple in an O_2-free system is described. This couple has been employed to reduce a variety of organic halides to hydrocarbons in water-containing ether solvents. This Zn–Cu preparation is exceptional in that reactions are carried out under mild conditions which are readily reproducible.

We wish to describe the use of an improved Zn–Cu couple for the reduction of organic halides in solvents containing H_2O or D_2O. Several groups have previously employed such a reaction.[1-3] This preparation differs from others in that all manipulations of the Zn–Cu are performed in an oxygen-free system.[4] The couple thus formed reacts with organic halides in ether solvents under mild and reproducible conditions.

Results and Discussion

A typical reduction was carried out as indicated in eq 1.

$$\underset{25\text{ mmol}}{\text{R–X}} + \underset{25\text{–}30\text{ mmol}}{D_2O} + \underset{100\text{ mmol}}{\text{Zn–Cu}} \xrightarrow[\text{solvent}]{\text{ether}} \text{R–D} \quad (1)$$

The Zn–Cu couple is formed from zinc dust and an acidic solution containing about 3 mol % cupric chloride. After its formation the metal is thoroughly washed with water to remove inorganic salts, with acetone to remove any remaining water, and finally with diethyl ether. After drying at room temperature under vacuum the metal is a very fine black powder. An excess of this material is employed.

Water-miscible ethers are the preferred solvents in this reaction. Convenience in the workup largely determines the choice of the particular ether. Representative examples are given in the Experimental Section.

Reductions which have been carried out by this method are shown in Table I. Activated alkyl halides react smoothly at room temperature (entries 1–9). Simple haloalkane require somewhat higher temperatures for reaction (entries 10–13). Aromatic and vinyl halides are even less reactive and typically require longer reaction times (entries 14–20). A primary tosylate (entry 21) does not react.

Clean monodeuteration (per halogen) is found in this reaction even in cases where deuterium incorporation by exchange might be anticipated (entries 1–7). This allows for the preparation of compounds not readily obtainable by other methods. For example, the conversion of ketones to their α-monodeuterio analogues can be readily accomplished by the preparation and purification of the monobromo derivative, followed by reduction with Zn–Cu in the presence of deuterium oxide.

Stereospecificity in the reduction of vinyl halides appears to depend on the system. The cis,cis isomer of 1,4-dichlorobutadiene reduces cleanly to the cis,cis isomer of 1,4-dideuteriobutadiene (entry 15). The other two isomers (entries 16 and 17) are less clean with the cis,trans isomer contaminated with about 1% of the others and trans,trans containing 13% cis,trans and 2% cis,cis. The simple vinyl iodide *trans*-1-iodo-1-heptene gives a mixture of *cis*-/*trans*-1-deuterio-1-heptene (entry 20). Additional work is needed before this feature can be understood.

Reaction of iodobenzene or 2-bromoheptane with Zn–Cu in the absence of water leads to a soluble species which yields hydrocarbon product on addition of H_2O. This suggests an organozinc species[5] although no attempt has been made as yet to isolate these intermediates.

Analysis. The product deuterium content was determined by conventional mass spectrometry or in many cases by an analysis of the ^{13}C nuclear magnetic resonance (^{13}C NMR) spectrum. A typical proton decoupled ^{13}C NMR spectrum consists of single lines, one for each magnetically nonequivalent carbon. Replacement of a proton with a deuteron results in a splitting of the carbon signal (J_{CD} is typically 20 Hz) and a change in chemical shift.[6] In general, for the saturated carbon signals examined, a 0.20–0.36-ppm upfield shift per directly bonded deuterium was observed (see supplementary material). Operationally this allows for the observation of a small amount of C–H impurity in the presence of C–D material. The method[7] can be made quantitative by integrating the spectrum under the proper machine conditions or, preferably, by recording the spectrum of a sample before and after spiking with a known amount of perprotio material. Figure 1 shows the methyl ^{13}C NMR region of toluene-d_1 both before and after the addition of 6 mol % toluene. This method of analysis is particularly effective if deuterium incorporation in the 90–100% range is encountered.[8]

Experimental Setion

Zinc dust was obtained from Fisher. Deuterium oxide (99.8% d_2) was obtained from Stohler Isotope Chemicals. Solvents were dried by standard procedures. Highest deuterium incorporations were obtained if the dried solvents were treated with a small portion of deuterium oxide and then redried before use. All reactions were performed in flame-dried glassware in an atmosphere of dry nitrogen. Magnetic resonance spectra were recorded using a Varian XL-100 or T-60 spectrometer and the data are reported using the δ scale relative to internal tetramethylsilane. Mass spectra were recorded on an Atlas MS-9, Varian Synchrotron, or Du Pont 21-490B mass spectrometer. Raman spectra were obtained using a Spex 1401 Raman double spectrometer. The exciting radiation was supplied by an argon laser operating at 4880 Å and 300 mW.

Zinc–Copper Couple. All steps in the Zn–Cu couple preparation were performed in an oxygen-free environment. Zinc dust (6.5 g, 100 mmol) was suspended in distilled water (10 ml). Acidic cupric chloride solution (0.15 M in 5% hydrochloric acid, 22 ml) was added with vigorous magnetic stirring. When the evolution of gas ceased the suspension was filtered and the black solid was washed with water until the wash gave a negative test with 6% silver nitrate solution. The Zn–Cu was then washed twice with acetone. Highest deuterium incorporations were obtained if the acetone washes were followed by a deuterium oxide wash and then two more acetone washes. Finally the Zn–Cu was washed twice with diethyl ether and dried under vacuum at room temperature. After drying the Zn–Cu was ready for the addition of solvent, deuterium oxide (~27 mmol), and substrate (~25 mmol).

1,4-Dideuteriobutadiene. Isomerically pure 1,4-dichloro-1,3-butadiene[9] (3 g, 25 mmol) was added to Zn–Cu (prepared from 15 g of zinc) in dioxane (50 ml) containing deuterium oxide (5 g, 250 mmol). The mixture was magnetically stirred and refluxed for 4 h while the 1,4-dideuterio-1,3-butadiene was trapped at −78 °C from a slow

Table I. Reductions of Alkyl Halides with Zn–Cu

	Halide	Registry no.	Product	Registry no.	Yield,[a] %	Conditions solvent, [b] °C, h	Method[c]	Deuterium analysis d_0	d_1	d_2
1.	2-Chlorocyclopentanone	694-28-0	Cyclopentanone-2-d_1	25415-09-2	71	TG, 25, 4	A	5	94	1
2.	3-Bromobutanone	814-75-5	2-Butanone-3-d_1	60595-38-2	67 (97)	TG, 25, 1	B	4	96	
3.	3-Bromo-2-heptanone	51134-59-9	2-Heptanone-3-d_1	60595-39-3	55 (67)	E, 25, 2	B	1	99	
4.	3-Bromocamphor	60595-36-0	*exo*-Camphor-3-d_1	60595-40-6	33	THF, 25, 2	C		100	
5.	Methyl chloroacetate	96-34-4	Methyl acetate-2-d_1	6181-03-9	64	TG, 25, 14	B	1	99	
6.	Methyl dichloroacetate	116-54-1	Methyl acetate-2,2-d_2	60595-41-7	47	TG, 25, 14	B			100
7.	Chloroacetonitrile	107-14-2	Acetonitrile-d_1	26456-53-1	71	TG, 25, 3	B	5	95	
8.	Benzyl bromide	100-39-0	Toluene-α-d_1	1861-00-3	55	TG, 25, 1.5	B		100	
9.	Benzal chloride	98-87-3	Toluene-α,α-d_2	17119-69-6	26	TG, 25, 2	B			100
10.	2-Bromoheptane	1974-04-5	Heptane-2-d_1	60595-42-8	80	TG, 25, 16	A	7	89	4
11.	2-Bromoheptane		Heptane	142-82-5	(100)	TG, 85, 16	D			
12.	1-Bromoadamantane	768-90-1	Adamantane	281-23-2	(89)	THF, 65, 32	D			
13.	(+)-2-Bromooctane	1191-24-8	(±)-Octane-2-d_1	60595-43-9	42	THF, 45, 16				
14.	2-Chloroacrylonitrile	920-37-6	Acrylonitrile-2-d_1	4635-82-9	57	TG, 25, 1	B		100	
15.	*cis,cis*-1,4-Dichlorobutadiene	3588-11-2	*cis,cis*-Butadiene-1,4-d_2	39768-32-6	70–90	D, 100, 4	A	0	4	96
16.	*cis,trans*-1,4-Dichlorobutadiene	3588-13-4	*cis,trans*-Butadiene-1,4-d_2 [d]	39768-59-7	85	D, 100, 4	A	1	9	90
17.	*trans,trans*-1,4-Dichlorobutadiene	3588-12-3	*trans,trans*-Butadiene-1,4-d_2 [d]	39768-65-5	80	D, 100, 4	A	1	16	83
18.	Iodobenzene	591-50-4	Benzene-d_1	1120-89-4	80	TG, 75, 16	B	10	90	
19.	Iodobenzene		Benzene	71-43-2	(45)	TG, 75, 16	D			
20.	*trans*-$C_5H_{11}CH$=CHI	60595-37-1	$C_5H_{11}CH$=CHD trans 65% cis 35%	60595-44-0	25	D, 100, 13	C		100	
21.	*n*-Octyl tosylate	3386-35-4		60595-45-1		THF, 65, 16				

[a] Yields in parentheses were determined by GC; all others are isolated yields. [b] Solvents: D = dioxane, TG = tetraglyme, E = diethyl ether, THF = tetrahydrofuran. [c] A = mass spectroscopy; B = ^{13}C NMR (see supplementary material); C = ^{1}H NMR; D = water was substituted for deuterium oxide. [d] Predominantly this isomer. See text.

Figure 1. The methyl region from the ^{13}C NMR spectrum of toluene-α-d_1. (A) before the addition of perprotiotoluene; (B) after the addition of 6 mol % perprotiotoluene. The arrow indicates the location of the new absorption.

stream of nitrogen. Isolated yields ranged from 70 to 90%: ^{1}H NMR δ 4.95 (terminal) and 6.27 (interior); Raman (neat) 1226 and 2260 cm^{-1} (see supplementary material); mass spectrum (12 eV) *m/e* (rel intensity) 57 (5), 56 (100, M$^+$), 55 (7); compare C_4H_6 mass spectrum (12 eV) *m/e* (rel intensity) 55 (5), 54 (100, M$^+$), 53 (5). The *cis,trans*- and *trans,trans*-1,4-dichlorobutadienes undergo a small amount of isomerization to the more stable cis,cis isomer under these conditions. Raman data for the three 1,4-dideuteriobutadiene isomers will be included in the supplementary material.

The following is a typical procedure for activated alkyl halides.

2-Butanone-3-d_1. 3-Bromo-2-butanone (3.8 g, 25 mmol) was added to Zn–Cu (prepared from 15 g of zinc) in tetraglyme (20 ml) containing deuterium oxide (0.5 ml). The mixture was magnetically stirred at room temperature for 1 h. A high-vacuum, closed system distillation followed by drying with magnesium sulfate yielded 2-butanone-3-d_1 (1.2 g, 67%): ^{1}H NMR δ 1.0 (d, 3 H), 2.1 (s, 3 H), 2.3 (m, 1 H); ^{13}C NMR δ 7.9 (s), 28.9 (s), 36.0 (t), 205.4 (s).

The following is a typical procedure for unactivated alkyl halides.

Octane-2-d_1. (+)-2-Bromooctane [1.15 g, 6 mmol, [α]D 27 (c = 1.74, ethanol)] was added to Zn–Cu (3.76 g) in tetrahydrofuran (20 ml) containing deuterium oxide (0.40 ml). The bromooctane also contained some carbon tetrabromide and bromoform which were also

reduced under these conditions. The mixture was heated at 45 °C for 16 h. The remaining Zn–Cu was removed by centrifugation and the supernatant liquid was added to water (100 ml) containing hydrochloric acid (0.5 ml). The water was extracted with pentane (4 × 2 ml), and the pentane was washed with 5% sodium bicarbonate solution and saturated sodium chloride solution. After drying with magnesium sulfate the product (0.285 g, 42%) was isolated by preparative GC (10 ft × 0.25 in. 5% OV-101 at 45 °C): $[\alpha]_D$ <0.04 (*c* 13.75, ethanol); mass spectrum (70 eV) *m/e* (rel intensity) 116 (5), 115 (51, M^+), 114 (3), 86 (58), 85 (66), 43 (100).

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Registry No.—Zn, 7440-66-6; Cu, 7440-50-8.

Supplementary Material Available. The Raman spectra and a table of normalized Raman intensities for the three isomeric 1,4-dideuteriobutadienes as well as ^{13}C NMR parameters for the deuterated products (3 pages). Ordering information is given on any current masthead page.

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Novel C_{19} Trienes from Abietic Acid in Fluorosulfonic Acid[1a,b]

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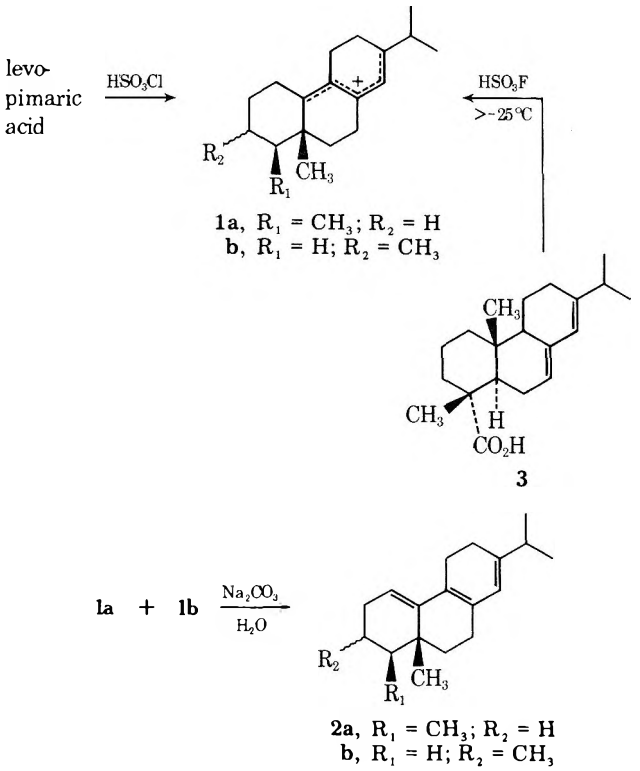
Abietic acid can be recovered from fluorosulfonic acid below −40 °C. At higher temperatures an irreversible rearrangement takes place (Scheme III) to give stable carbocations **1a** and **1b**. Quenching the cations in aqueous sodium carbonate afforded a 1:2 mixture of trienes **2a** and **2b** whose structures were established by their spectroscopic properties, the degradation shown in Scheme I, and the independent synthesis of key degradation products shown in Scheme II.

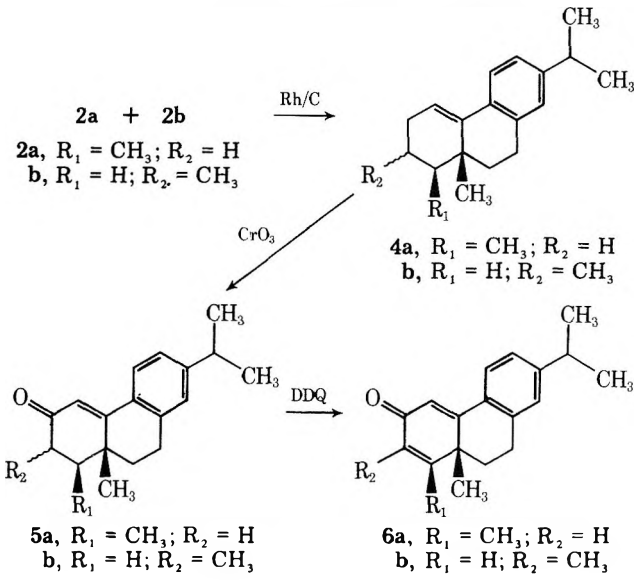
The reaction of levopimaric acid in the carbocation-stabilizing solvent chlorosulfonic acid to give cations **1a** and **1b**, and, after quenching, trienes **2a** and **2b**, has been reported by Mehta and Kapoor.[2] These authors referred to our independent investigation of the reaction of abietic acid (**3**) in fluorosulfonic acid above −25 °C to give the same cations and trienes. Although our report of our work was delayed in the refereeing and rewriting process, we would like to describe some aspects of it now, since a detailed account has not yet appeared, the structural conclusions of Mehta and Kapoor depend to some extent on comparison with our compounds, and some interesting and perhaps generally useful synthetic work was done in the course of our investigation.



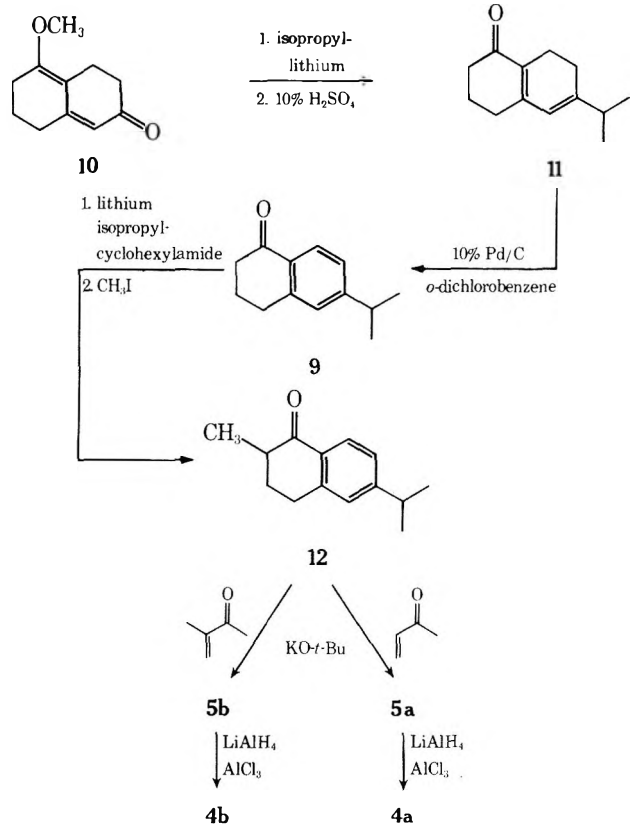
The preparation and spectroscopic properties of the cations and trienes have already been described and interpreted in the literature,[2] and our very similar results are described in detail in the Experimental Section. Therefore, we will confine our discussion primarily to the structure determination of trienes **2a** and **2b**,[3] outlined in Scheme I, and the synthesis of the degradation products, the styrenes, **4a** and **4b**, and the enones, **5a** and **5b**, outlined in Scheme II.

Structure Determination. Our degradative scheme differs somewhat from that of Mehta and Kapoor in that we were able to separate the trienes **2a** and **2b** by chromatography on a silver nitrate–alumina column[4] and obtain styrenes **4a** and **4b**, respectively, from them by rhodium on carbon dehydrogenation.[5] The other workers obtained a mixture of styrene **4a** and a further dehydrogenation product of **4b** on palladium–carbon dehydrogenation of the triene mixture. The position of the tertiary methyl group (R_1 or R_2) in "ring A" of the styrenes was established in our work by oxidation of **4a** and **4b** to the enones **5a** and **5b**, respectively, and dehydrogenation of these to their respective dienones **6a** and **6b**. The α hydrogen (R_2) on the dienone **6a** appeared at higher field

Scheme I. Degradation of Trienes 1a and 1b

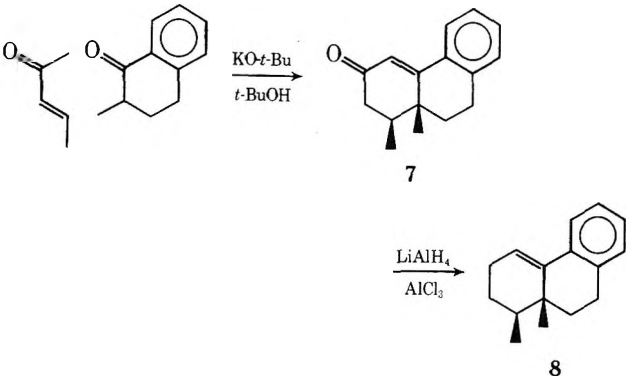


Scheme II. Synthesis of Some Degradation Products from Trienes 1a and 1b



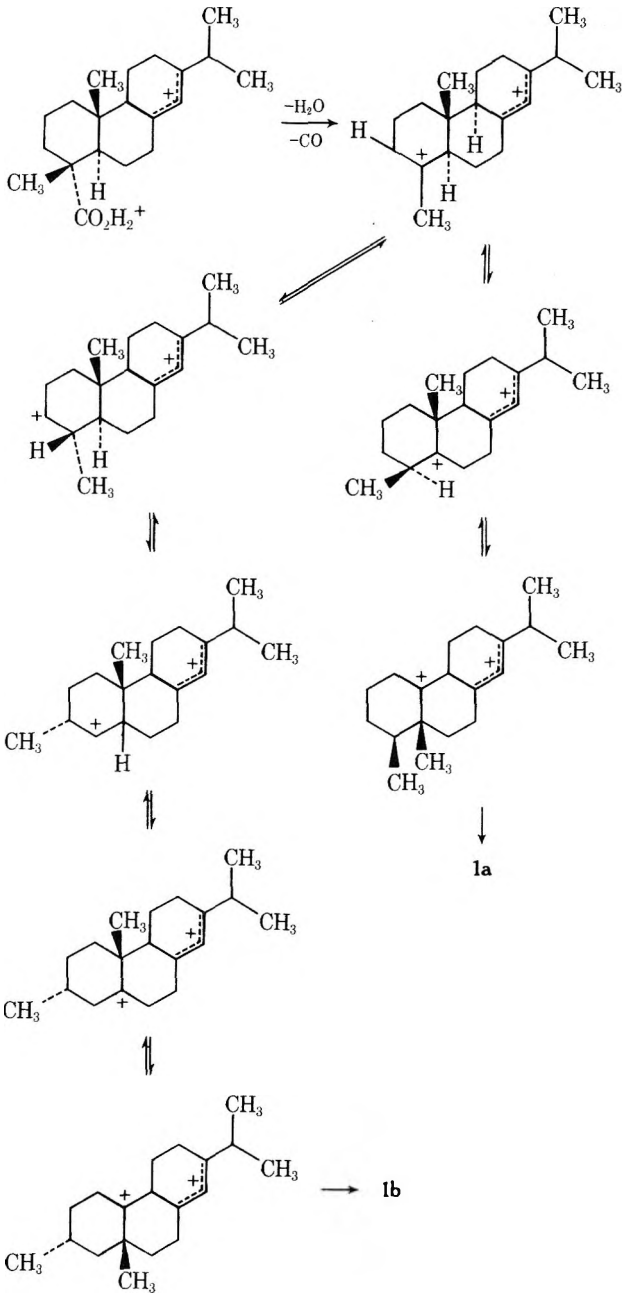
in the ^1H NMR (δ 6.04) than the β hydrogen (R_1) of **6b** (δ 6.48), while the β-methyl (R_1) of **6a** appeared at lower field (δ 2.03) than the α-methyl (R_2) of **6b** (δ 1.86), consistent with our structural assignment.[6] The remaining spectroscopic properties of all the degradation products (IR, UV, MS) were consistent with the assigned structures, as were the combustion analyses, and all were optically active.[8] Although the structures appeared to be reasonably well secured, we chose to obtain further evidence by independent synthesis of some key degradation products.

Syntheses. The syntheses of **4a**, **4b**, **5a**, and **5b** in Scheme II are patterned after the Whitlock syntheses of some related compounds, **7** and **8**, lacking the isopropyl group.[7]



Although the tetralone **9** required for our synthesis had been reported,[10] we found it convenient to prepare this compound by the alternate route in Scheme II, which makes use of enol ether **10** reported by Patterson and Reusch,[11] and Nazarov and Zavyalov.[12] The syntheses require no comment, although it might be noted that the reconversion of **5a** and **5b** to **4a** and **4b** by Cava's method[13] provides reassurance that no deep-

Scheme III



seated structural reorganization took place in the reverse degradative transformation.

Mechanism. We agree with Mehta and Kapoor on the essential features of a plausible mechanism for the transformation of abietic acid to cations **1a** and **1b**, diagrammed in more detail in Scheme III. Separation of the isomeric trienes **2a** and **2b** has enabled us to demonstrate that cations **1a** and **1b** can be re-formed from their respective trienes in fluorosulfonic acid and are not interconverted at room temperature. We therefore suggest that the last step in the formation of each of these cations in Scheme III, which generates the dienylic cation from a dication, is irreversible, while all previous steps are reversible. It is possible that the wandering methyl group at C_2 in cation **1b** may have made still further excursions to C_3 and C_4 and we just did not isolate the resultant products from our mixture. However, the absence of any NMR peaks in the spectrum of the cation mixture from abietic acid not also present in the spectra of the individual cations prepared from their trienes, and the absence of significant peaks in the GC of the triene mixture other than those of the trienes **2a** and **2b**, limit the amount of such further rearrangement to no more than 10%. Such restriction of the freedom of the methyl group probably simply reflects the availability of the rapid, irreversible formation of **1b**, which drains the cations away before they have time to experiment further. Note that the mechanism predicts a cis disposition of the 1,10 methyl groups in **1a**, as observed, and a trans disposition of the 2,10 methyls in **1b** as is most probably the case based on the synthesis of **5b**.

Experimental Section

General. All melting points were taken on a Thomas-Hoover apparatus. Infrared spectra were recorded as neat films on a Perkin-Elmer 237B spectrophotometer, and ultraviolet spectra in methanol solutions on a Unicam SP800 spectrophotometer. Nuclear magnetic resonance spectra were taken on Varian T-60 and Varian HA-100 spectrometers. Tetramethylammonium tetrafluoroborate (τ 6.87[14]) was used as an internal standard for all carbocation spectra, and tetramethylsilane was used as an internal standard for all other spectra. A Hitachi RM-U6 spectrometer was used to obtain all mass spectra.

Purification of Abietic Acid. Abietic acid was prepared from N-grade wood rosin (Hercules Powder Co.) by Sanderson and Weldy's modification of the *Organic Syntheses* procedure.[15,16] Thus, the N-grade wood rosin was refluxed in glacial acetic acid for 3 h, and the resultant mixture of resin acids, "Steele's acids", was recrystallized from ethyl acetate. Isolation of the major component, abietic acid, was achieved by the preparation and subsequent acetone recrystallizations (five) of the di-*n*-amylamine salt. The free acid was then generated by treating a cold ethanolic solution of the amine salt with acetic acid. Addition of water precipitated the abietic acid which was recrystallized from acetone–water to give colorless crystals (mp 171–174 °C) in 10–15% yield.

Quenching of the Abietic Acid −40 °C Cation. Regeneration of Abietic Acid. A solution of abietic acid in fluorosulfonic acid which had been warmed to −40 °C was quenched in aqueous sodium carbonate. The solution was acidified with dilute hydrochloric acid and extracted with ether to give abietic acid in approximately 80% recovery.

Rearrangement of Abietic Acid in Fluorosulfonic Acid. Isolation of *cis*-1,10a-Dimethyl-7-isopropyl-1,2,3,5,6,9,10,10a-octahydrophenanthrene (2a) and 2,10a-Dimethyl-7-isopropyl-1,2,3,5,6,9,10,10a-octahydrophenanthrene (2b). Using the procedure described previously a solution of 10.0 g (0.033 mol) of abietic acid in 80 ml of fluorosulfonic acid was prepared and warmed to 25 °C for 2 h. As the solution was warmed from −78 °C it turned from a bright yellow to a deep burgundy and gas evolution was noticed. It was again cooled to −78 °C and quenched in 1400 ml of aqueous sodium carbonate containing 200 ml of hexane. The hexane layer was removed, and the aqueous phase extracted twice with 200 ml of hexane. Removal of the solvent gave 7.7 g (91%) of a yellow oil.

A portion of this oil, 1.60 g, was adsorbed on a 28 × 2.2 cm column of 20% silver nitrate impregnated alumina. Elution with 200 ml of hexane gave 100 mg of a colorless oil which was a complex hydrocarbon mixture (NMR) and was not investigated further. Elution with 400 ml of 1:4 benzene–hexane gave 850 mg (53%) of a yellow oil which contained **2a** and **2b** as the major products in a ratio of approximately 1:2 (GLC). Preparative GLC (230 °C, 5 ft × 0.38 in. column of 20% Carbowax 20M on Anakrom 40–100 mesh) afforded two major fractions.

Fraction 1 contained **2b** with a 10% impurity of **4b** (NMR). These were separated by column chromatography. Thus, 73 mg of fraction 1 was adsorbed on a 15 × 1.0 cm column of 20% silver nitrate impregnated alumina. The column was eluted with 30 ml of 2% ether–hexane, then 5% ether–hexane until UV analysis indicated that all of **4b** had been removed. Elution with 50 ml of 1:4 benzene–hexane gave 45 mg of **2b** as a light yellow oil: IR (neat film) 1648 cm^{-1}; UV λ_{max} (MeOH) 298 nm (ϵ 22 100); NMR δ (CCl_4) 5.47 (1 H, m), 5.43 (1 H, s), 1.04 (6 H, d, J = 7 Hz), 0.98 (3 H, s), 0.96 (3 H, d, $J_{apparent}$ = 7 Hz); MS *m/e* (rel intensity) 256 (M^+, 100), 241 (56), 214 (20), 213 (58).

Fraction 2 contained **2a** and 30% **4b** (NMR). Column chromatography of 41 mg by the procedure described for **2b** gave 20 mg of **2a** as a light yellow oil: IR (neat film) 1648 cm^{-1}; UV λ_{max} (MeOH) 300 nm (ϵ 23 100); NMR δ (CCl_4) 5.52 (1 H, t, J = 4 Hz), 5.43 (1 H, s), 1.04 (6 H, d, J = 7 Hz), 0.98 (3 H, d, $J_{apparent}$ = 6 Hz), 0.93 (3 H, s); MS *m/e* (rel intensity) 256 (M^+, 100), 241 (51), 214 (13), 213 (53).

Cations of *cis*-1,10a-Dimethyl-7-isopropyl-1,2,3,5,6,9,-10,10a-octahydrophenanthrene (2a) and 2,10a-Dimethyl-7-isopropyl-1,2,3,5,6;9,10,10a-octahydrophenanthrene (2b) in Fluorosulfonic Acid. Solutions of **2a** and **2b** in fluorosulfonic acid were prepared at −78 °C and their NMR spectra recorded at −30 and 25 °C. The spectra did not change with temperature. **2a:** NMR δ (FSO_3H) 6.93 (1 H, s), 1.31 (6 H, d, J = 7 Hz), 1.26 (3 H, s), 1.05 (3 H, d, $J_{apparent}$ = 5 Hz). **2b:** NMR δ (FSO_3H) 6.93 (1 H, s), 1.40 (3 H, s), 1.31 (6 H, d, J = 7 Hz), 1.00 (3 H, d, J = 6 Hz).

Dehydrogenation of the Abietic Acid–Fluorosulfonic Acid Rearrangement Product. Isolation of *cis*-1,10a-Dimethyl-7-isopropyl-1,2,3,9,10,10a-hexahydrophenanthrene (4a) and 2,10a-Dimethyl-7-isopropyl-1,2,3,9,10,10a-hexahydrophenanthrene (4b). The crude rearrangement product, 4.82 g (0.019 mol), was dissolved in 100 ml of *o*-xylene, and to it was added 2.0 g of 5% rhodium on carbon. The mixture was heated with stirring and 20 ml of xylene was distilled to remove traces of water. The distilling head was replaced with a condenser equipped with a nitrogen inlet, and the mixture was heated at reflux for 15 h after which time it was cooled to room temperature and the catalyst removed by filtration. The solvent was removed under vacuum leaving 4.67 g of a dark yellow oil.

Most of the above product, 4.39 g, was adsorbed on a 400 g (45 × 3 cm) column of 20% silver nitrate impregnated alumina. Elution with 500 ml of hexane gave 1.10 g (25%) of a colorless oil containing ii and iii (footnote 5) as the major products (GLC, NMR) in a ratio of 3.4:4.8. Elution with 1:4 benzene–hexane (500 ml) gave 2.07 g (47%) of a light yellow oil. Analysis by GLC showed two major components in a ratio of 3.5:2.8.

Preparative GLC (230 °C, 5 ft × 0.38 in. column of 20% Carbowax 20M on Anakrom 40–100 mesh) afforded **4b** as the first component: mp 76–77 °C; $[\alpha]^{25}D$ −68°; IR (neat film) 1635 cm^{-1}; UV λ_{max} (MeOH) 256 nm (ϵ 16 700); NMR δ (CCl_4) 7.27 (1 H, d, J = 8 Hz), 6.84 (1 H, br d, J = 8 Hz), 0.99 (3 H, s), 0.98 (3 H, d, $J_{apparent}$ = 6 Hz); MS *m/e* (rel intensity) 254 (M^+, 100), 249 (99), 211 (92), 169 (32), 141 (31).

Anal. Calcd: C, 89.70; H, 10.30. Found: C, 89.73; H, 10.30.

The second component was **4a**: bp 125–130 °C (0.4 mm); $[\alpha]^{25}D$ −91°; IR (neat film) 1635 cm^{-1}; UV λ_{max} (MeOH) 256 nm (ϵ 17 400); NMR δ (CCl_4) 7.27 (1 H, d, J = 8 Hz), 6.84 (1 H, br d, J = 8 Hz), 6.79 (1 H, br s), 6.01 (1 H, t, J = 4 Hz), 1.20 (6 H, d, J = 7 Hz), 0.94 (3 H, d, $J_{apparent}$ = 6 Hz), 0.84 (3 H, s); MS *m/e* (rel intensity) 254 (M^+, 100) 249 (92 211 (68), 169 (37), 141 (50).),

Anal. Calcd: C, 89.70; H, 10.30. Found: C, 89.56; H, 10.26.

Individual Dehydrogenations of 2a and 2b. When **2b** (44 mg) was dehydrogenated under the above conditions there was obtained 39 mg of a yellow oil containing **4b** (NMR, GLC) as the major component. Similarly 18 mg of **2a** gave 14 mg containing **4a**.

Oxidation of 4a and 4b. Preparation of *cis*-1,10a-Dimethyl-7-isopropyl-1,9,10,10a-tetrahydro-3(2*H*)-phenanthrone (5a) and 2,10a-Dimethyl-7-isopropyl-1,9,10,10a-tetrahydro-3(2*H*)-phenanthrone (5b). In a flask equipped with a mechanical stirrer and a nitrogen inlet were placed 30.0 g (0.38 mol) of pyridine and 250 ml of methylene chloride. To this was added with stirring 19.0 g (0.10 mol) of chromium trioxide (dried over phosphorus pentoxide under vacuum) in small portions over a 20-min period. The solution was stirred for an additional 15 min, and to it was added 3.18 g (0.012 mol) of the 2.8:3.5 mixture of **4a** and **4b**. After 1.5 h the methylene chloride

solution was decanted, and the flask washed twice with 100 ml of ether. The combined solutions were washed with three 100-ml portions of 5% sodium hydroxide, 5% hydrochloric acid, and 10% sodium carbonate, respectively. After drying over sodium sulfate the solvent was removed to give 2.31 g of a dark red oil.

The product was adsorbed on a 45 × 3 cm column of silica gel, and the column eluted with 500 ml portions of 1:9, 1:4, 3.3:6.7, and 2:3 ether–hexane, respectively, with 25-ml fractions being collected. Fractions 39–43 were combined to give 193 mg (~10%) of **5b** (80% pure by NMR and GLC). An analytical sample was obtained by preparative TLC on silica gel eluted with 1:1 ether–hexane as a light yellow oil which was evaporatedly distilled at 100 °C (0.4 mm): $[\alpha]^{25}D$ −277°; IR 1660 and 1585 cm^{-1}; UV λ_{max} (MeOH) 304 nm (ϵ 26 200); NMR δ (CCl_4) 7.57 (1 H, d, J = 8 Hz), 7.01 (1 H, br d, J = 8 Hz), 6.95 (1 H, br s), 6.28 (1 H, s), 1.24 (6 H, d, J = 7 Hz), 1.21 (3 H, s), 1.12 (3 H, d, J = 6 Hz); MS m/e (rel intensity) 268 (M^+, 10), 226 (100), 184 (57), 169 (39), 155 (39), 141 (43).

Anal. Calcd: C, 85.02; H, 9.01. Found: C, 84.97; H, 8.94.

Fractions 55–63 gave 360 mg (30%) of **5a** (90% pure by NMR and GLC). An analytical sample was obtained by preparative TLC on silica gel eluted with 3:1 ether–hexane as a light yellow oil which was evaporatedly distilled at 100 °C (0.4 mm): $[\alpha]^{25}D$ −263°; IR 1660 and 1585 cm^{-1}; UV λ_{max} (MeOH) 306 nm (ϵ 21 100); NMR δ (CCl_4) 7.59 (1 H, d, J = 8 Hz), 7.01 (1 H, br d, J = 8 Hz), 6.95 (1 H, br s), 6.34 (1 H, s), 1.24 (6 H, d, J = 7 Hz), 1.04 (3 H, d, J = 6.5 Hz), 1.02 (3 H, s); MS m/e (rel intensity) 268 (M^+, 67), 226 (100), 184 (55), 169 (34), 155 (38), 141 (41). The 2,4-dinitrophenylhydrazone had mp 265 °C dec.

Anal (2,4-DNP). Calcd: C, 66.94; H, 6.29; N, 12.49. Found: C, 66.62; H, 6.35; N, 12.40.

Individual Oxidations of 4a and 4b. Oxidation of **4b** (88 mg) with chromium trioxide–pyridine complex under the above conditions provided 10 mg of **5b**. Similarly 52 mg of **4a** gave 14 mg of **5a**.

Dehydrogenation of 5b. Preparation of 2,10a-Dimethyl-7-isopropyl-9,10-dihydro-3(10a*H*)-phenanthrone (6b).[7] A solution of 70 mg (0.26 mmol) of **5b** and 70 mg (0.27 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 15 ml of dry dioxane was cooled to 10 °C, and hydrogen chloride was bubbled through it for 5 s. The solution was stirred at room temperature for 2 h after which time an additional 40 mg (0.17 mmol) of DDQ was added and the reaction heated at reflux for 1 h. After it had been cooled to room temperature the reaction mixture was poured on to a 10 × 1 cm column of activity II alumina, and the column eluted with 75 ml of ether. The solvent was removed to give 60 mg of a light orange oil which was purified by preparative TLC on alumina eluted with 2:1 ether–hexane to give 35 mg (50%) of **6b**. The light yellow oil was evaporatively distilled at 90 °C (0.3 mm): $[\alpha]^{25}D$ −101°; IR (neat film) 1660, 1625, and 1600 cm^{-1}; UV λ_{max} (MeOH) 315 nm (ϵ 12 500); NMR δ (CCl_4) 7.53 (1 H, d, J = 8 Hz), 7.04 (1 H, br d, J = 8 Hz), 6.96 (1 H, br s), 6.48 (1 H, q, J = 1.5 Hz), 1.18 (3 H, s); MS m/e (rel intensity) 266 (M^+, 100), 251 (84), 238 (68), 223 (81).

Dehydrogenation of 5a. Preparation of 1,10a-Dimethyl-7-isopropyl-9,10-dihydro-3(10a*H*)-phenanthrone (6a). Following the same procedure as described for **5b**, 70 mg of **5a** gave, after preparative TLC on alumina eluted with 3:1 ether–hexane, 30 mg (43%) of **6a** as a light yellow oil which was evaporatively distilled at 90 °C (0.3 mm): $[\alpha]^{25}D$ −119°; IR 1660, 1625, and 1600 cm^{-1}; UV λ_{max} (MeOH) 315 nm (ϵ 13 700); NMR δ (CCl_4) 7.53 (1 H, d, J = 8 Hz), 7.04 (1 H, br d, J = 8 Hz), 6.96 (1 H, br s), 6.43 (1 H, d, J = 1.7 Hz), 6.04 (1 H, m), 2.03 (3 H, d, J = 1.5 Hz), 1.24 (6 H, d, J = 7 Hz), 1.25 (3 H, s); MS m/e (rel intensity) 266 (M^+, 70), 251 (32), 238 (84), 223 (100).

6-Isopropyl-3,4,7,8-tetrahydro-1(2*H*)-naphthalenone (11). To 50 ml of ether which had been cooled to −78 °C under a nitrogen atmosphere was added 17.5 ml (0.035 mol) of 2 M isopropyllithium in pentane (ROC/RIC Chemical Corp.). A solution of 5.34 g (0.03 mol) of enol ether **10**[11,12] in 50 ml of ether was then added dropwise over a 15-min period. The mixture was stirred at −78 °C for 1 h, and 100 ml of 10% sulfuric acid was added. After stirring for 15 min the ether layer was removed, and the aqueous phase was extracted with 100 ml of ether. The ether solutions were combined, and washed twice with 100 ml portions of water, 5% sodium bicarbonate, and saturated potassium chloride solution. The solvent was removed, and the product was evaporatively distilled at 50 °C (0.3 mm) to give 2.91 g of a nearly colorless oil.

The product was adsorbed on silica gel (45 × 3 cm column), the column was eluted with 1:4 ether–hexane, and 20-ml fractions were collected. Fractions 31–50 were combined to give 1.83 g (32%) of **11** of approximately 90% purity (NMR). An analytical sample was obtained from preparative TLC on alumina eluted with 3:1 ether–hexane as a colorless oil: IR 1660 and 1580 cm^{-1}; UV λ_{max} (MeOH) 315 nm (ϵ 11 300); NMR δ (CCl_4) 5.68 (1 H, br s), 1.08 (6 H, d, J = 7 Hz); MS m/e (rel intensity) 190 (M^+, 17), 148 (36), 147 (100), 91 (57). The 2,4-dinitrophenylhydrazone had mp 208–209 °C.

Anal (2,4-DNP). Calcd: C, 61.61; H, 5.97; N, 15.13. Found: C, 61.48; H, 6.05; N, 15.16.

6-Isopropyl-3,4-dihydro-1(2*H*)-naphthalenone (9). In a 250-ml three-neck flask equipped with a nitrogen inlet, condenser, and distilling head were placed 3.0 g of 10% palladium on carbon and 100 ml of *o*-dichlorobenzene (ODCB). The mixture was heated to reflux, and 20 ml of ODCB distilled to remove traces of water. A solution of 1.7 g (8.9 mmol) of **11** in 50 ml of ODCB was added dropwise over a 1-h period. After the addition was complete the solution was heated for an additional 30 min, cooled to room temperature, and the catalyst removed by filtration. The solvent was removed under vacuum leaving a yellow oil which was evaporatively distilled at 45 °C (0.3 mm) to give 1.20 g (72%) of **9** of greater than 90% purity (GLC). A pure sample was obtained from preparative GLC (220 °C, 6 ft × 0.25 in. column of 20% SE-30 on Chromosorb W): IR 1680 and 1605 cm^{-1}; UV λ_{max} (MeOH) 259 nm (ϵ 16 200); NMR δ (CCl_4) 7.93 (1 H, d, J = 8 Hz), 7.14 (1 H, br d, J = 8 Hz), 7.03 (1 H, br s), 1.29 (6 H, d, J = 7 Hz); MS m/e (rel intensity) 188 (M^+, 74), 173 (100), 160 (81), 145 (44). The 2,4-dinitrophenylhydrazone had mp 195–196 °C (lit. mp 196.0–196.3 °C).[10]

6-Isopropyl-2-methyl-3,4-dihydro-1(2*H*)-naphthalenone (12).[18] To 1.7 ml (2.8 mmol) of 1.67 M *n*-butyllithium in hexane was added, under a nitrogen atmosphere, 0.48 ml (2.8 mmol) of isopropylcyclohexylamine. The contents were stirred for 10 min with most of the hexane being removed with a stream of nitrogen. The flask was cooled to 0 °C, and 4 ml of tetrahydrofuran was added. A solution of 480 mg (2.6 mmol) of **9** in 3 ml of tetrahydrofuran was added dropwise over a 1-min period, and the solution was stirred for 5 min. Methyl iodide (1.7 g, 12.2 mmol) was then added rapidly. The ice bath was removed, and the reaction mixture was stirred for 1 h at room temperature. After this time 15 ml of 10% hydrochloric acid was added, and the product was extracted with two 25-ml portions of hexane. The hexane extract was washed with water and 10% sodium carbonate, and dried over sodium sulfate. The solvent was removed, and the product was chromatographed on a 25 × 1.5 cm column of activity II alumina. The column was eluted with 1:9 ether–hexane, and 15-ml fractions were collected. Fractions 5–8 were combined to give 400 mg (78%) of **12**: mp 41–42 °C (from hexane, low temperature); IR 1680 and 1605 cm^{-1}; UV λ_{max} (MeOH) 257 nm (ϵ 18 700); NMR δ (CCl_4) 7.93 (1 H, d, J = 8 Hz), 7.03 (1 H, br s), 1.29 (6 H, d, J = 7 Hz), 1.23 (3 H, d, J = 7 Hz); MS m/e (rel intensity) 202 (M^+, 44), 188 (20), 173 (22), 160 (100).

Anal. Calcd: C, 83.12; H, 8.97. Found: C, 83.10; H, 8.90.

Fractions 10–16 gave 70 mg of the starting tetralone.

***cis*-1,10a-Dimethyl-7-isopropyl-1,9,10,10a-tetrahydro-3-(2*H*)-phenanthrone (5a) from *trans*-3-Penten-2-one and 6-Isopropyl-2-methyl-3,4-dihydro-1(2*H*)-naphthalenone (12).** A solution of potassium *tert*-butoxide in *tert*-butyl alcohol was prepared by adding 30 mg (0.77 mmol) of potassium metal to 2 ml of *tert*-butyl alcohol (distilled from calcium hydride). To this was added 100 mg (0.50 mmol) of **12** in 1 ml of *tert*-butyl alcohol. After stirring for 15 min the solution was cooled with an ice bath until the solvent began to freeze, and 63 mg (0.75 mmol) of *trans*-3-penten-2-one[19] in 1 ml of *tert*-butyl alcohol was added. The reaction mixture was stirred for 20 h, after which water was added, and the product was extracted with two 20-ml portions of ether. Preparative TLC on silica gel eluted with 2:1 ether–hexane followed by molecular distillation [trace impurities at 50 °C (0.3 mm), and **5a** at 100 °C (0.3 mm)] gave 48 mg (36%) of **5a** whose spectral properties were identical with those obtained for material isolated from the oxidation of **4a**.

2,10a-Dimethyl-7-isopropyl-1,9,10,10a-tetrahydro-3(2*H*)-phenanthrone (5b) from 3-Methyl-3-buten-2-one and 6-Isopropyl-2-methyl-3,4-dihydro-1(2*H*)-naphthalenone (12). To a solution of 0.77 mmol of potassium *tert*-butoxide in 2 ml of *tert*-butyl alcohol was added 100 mg (0.50 mmol) of **12** in 1 ml of *tert*-butyl alcohol. After stirring for 15 min the solution was cooled with an ice bath until the solvent began to freeze, and 100 mg (1.2 mmol) of 3-methyl-3-buten-2-one (distilled from Pfaltz and Bauer material) in 1 ml of *tert*-butyl alcohol was added. After stirring for 20 h water was added, and the mixture was extracted with two 20-ml portions of ether. Preparative TLC on silica gel eluted with 1:1 ether–hexane followed by molecular distillation at 100 °C (0.3 mm) gave 55 mg (41%) of **5b** whose spectral properties were identical with those obtained for the oxidation product of **4b**.

2,10a-Dimethyl-7-isopropyl-1,2,3,9,10,10a-hexahydrophenanthrene (4b) from Reduction of 5b.[13] To a solution of 40 mg (0.15 mmol) of **5b** in 5 ml of ether was added 40 mg (0.30 mmol) of aluminum chloride followed after 1 min by 11 mg (0.30 mmol) of lithium aluminum hydride. The solution was stirred for 2 h, several drops of

water were added, and stirring was continued for 15 min. One gm of potassium sodium tartrate was then added, and the reaction mixture was filtered. The solid residue was washed several times with ether. The ether was removed, and the product was adsorbed on a 7 × 0.5 cm column of activity II alumina. Elution with hexane (20 ml) gave 28 mg (75%) of **4b** whose spectral properties were identical with those of the derivative obtained from the abietic acid rearrangement.

***cis*-1,10a-Dimethyl-7-isopropyl-1,2,3,9,10,10a-hexahydrophenanthrene (4a) from Reduction of 5a.** Following a procedure which was identical with that described for **4b**, 40 mg of **5a** gave 26 mg (69%) of **4a** whose spectral properties were identical with those for the derivative obtained from the abietic acid rearrangement.

Acknowledgment. We thank the Hercules Powder Co. for a generous sample of N-grade Rosin.

Registry No.—**2a,** 60606-84-0; **2b,** 60606-85-1; **3,** 514-10-3; **4a,** 49815-77-2; **4b,** 60606-86-2; **5a,** 60606-87-3; **5a** 2,4-DNP, 60606-88-4; **5b,** 60606-89-5; **6a,** 60606-90-8; **6b,** 60606-91-9; **9,** 60606-92-0; **10,** 51238-73-4; **11,** 60606-93-1; **11** 2,4-DNP, 60619-77-4; **12,** 60606-94-2; *trans*-3-penten-2-one, 3102-33-8; 3-methyl-3-buten-2-one, 814-78-8.

References and Notes

(1) (a) Supported by the National Science Foundation under Grants GP-10734 and GP-27994. (b) Abstracted in part from the Ph.D. Thesis of F. A. Mader, Michigan State University, 1972. (c) Dow Chemical Co. Summer Fellow, 1972.
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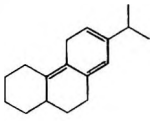
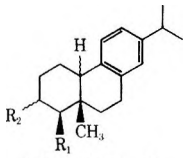
(3) The alternate arrangement of double bonds (i) considered by Mehta and



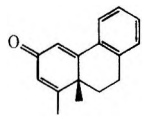
i

Kapoor[2] for trienes **1a** and **1b** is also compatible with all the data available to us.
(4) Like Mehta and Kapoor,[2] we observed decomposition of the trienes on attempted chromatography on $AgNO_3$–SiO_2.
(5) We also obtained the aromatic hydrocarbons ii and iii obtained by Mehta



ii, $R_1 = CH_3$; $R_2 = H$
iii, $R_1 = H$; $R_2 = CH_3$

and Kapoor, also isolated by catalytic hydrogenation of styrenes **4a** and **4b**.
(6) The ^1H NMR of **6a** is very similar to that of the model compound iv.[7]



iv

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Fluorine-19 Nuclear Magnetic Resonance. Electric Field Shifts of Bicyclic Fluorides

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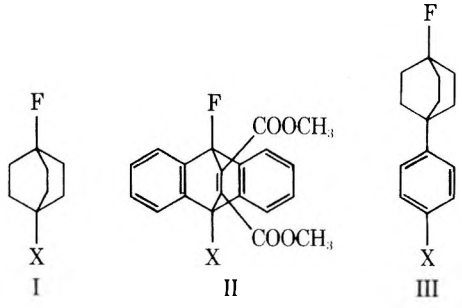
A number of 1-fluoro-4-para-substituted phenylbicyclo[2.2.2]octanes have been synthesized and their ^{19}F NMR spectra recorded. Significant *upfield* substituent chemical shifts (SCS) are observed for strong electron-withdrawing dipolar and charged substituents in a situation where substituent-induced structural effects cannot be invoked. The results strongly suggest that the previous interpretation of "anomalous" ^{19}F SCS for 4-substituted bicyclo[2.2.2]octyl-1-fluorides in terms of structural effects alone requires reappraisal. Further, the results impinge importantly on the factors determining ^{19}F chemical shifts in general.

Substituent-induced *upfield* shifts have been detected by Anderson and Stock[1] for a limited number of 1-fluoro-4-substituted bicyclo[2.2.2]octanes (I, X = F and $COOC_2H_5$).



A consideration of several factors by these workers led to the conclusion that these substituent chemical shifts (SCS)[2] are anomalous and probably a consequence of substituent-induced structural deformation of the flexible bicyclooctyl skeletal framework rather than a manifestation of dipolar electrostatic-field effects: (1) upfield SCS are not in accord with preconceptions regarding the electron-withdrawing influence of dipolar substituents on chemical shifts; (2) ^{19}F chemical shifts of various unsubstituted bicyclic fluorides are structurally dependent; (3) the fact that substituents do measurably alter the structure of the more rigid bicyclo[2.2.1]-heptyl system; and (4) the observation that ^{19}F substituent chemical shifts (SCS) for the more rigid dibenzobicyclo[2.2.2]-octyl derivatives, in particular, adducts of 10-substituted 9-

fluoroanthracenes with dimethyl acetylenedicarboxylate (II), are in the anticipated *low-field* direction as well as corresponding reasonably well to the σ_I scale.

However, because inverse-substituent behavior by ^{19}F chemical shifts is known for some aliphatic fluorides[3] where structural effects cannot be invoked, we decided to examine a new model system (III, 1-fluoro-4-para-substituted phenylbicyclo[2.2.2]octanes) in order to determine unambiguously the "normal" response of ^{19}F chemical shifts for bicyclooctyl[2.2.2]fluorides to the electrostatic-field effect of remote polar groups. In this regard, the new system is superior to I since substitution is not being effected on a carbon atom which is incorporated directly in the bicyclooctyl skeletal framework, thus, substituent-induced structural effects are entirely eliminated. Further, unlike system II, the electronic structure of the chemical bonds in the immediate vicinity of the fluorine atom are similar to I, i.e., F–C (sp^3) *not* F–C (sp^2). Here we report our findings for system I.

A scrutiny of the data listed in Table I leads to a number of important conclusions. Firstly, it is clear that ^{19}F chemical shifts for system III, and thus system I, respond to an applied electric field in the *opposite* sense to expectations based on traditional ideas regarding the direction of chemical shifts induced by electron withdrawal or donation. This is dramatically exemplified by the relatively large positive SCS (*upfield* shift) listed for the powerful inductive monopole, NH_3^+.

Secondly, it can be seen that the SCS for Br ($\sigma_I = 0.44$; $\sigma_R^0 = -0.19$; $\sigma_{R(BA)} = -0.19$)[4] is significantly more positive than that for F ($\sigma_I = 0.50$; $\sigma_R^0 = -0.34$; $\sigma_{R(BA)} = -0.45$)[4] in both benzene and DMF, while the SCS for NH_2 ($\sigma_I = 0.12$; $\sigma_R^0 = -0.48$; $\sigma_{R(BA)} = -0.82$),[4] a weak dipolar substituent, is *negative*. The origin of these trends clearly lies in a significant contribution to the applied electric field at the CF bond by the charges set up in the phenyl π system through mesomeric interaction with the substituent (mesomeric-field effect[5] or secondary resonance effect[6]). Thus, while the electron-withdrawing primary field effect emanating from the polar substituent–substrate bond and the mesomeric-field effect are opposed for +F−M substituents (NH_2, Br, and F), they must reinforce one another for +F+M substituents (NO_2 and CN). This point is formalized by the fact that a dual substituent parameter (DSP) analysis[4,6,7] (eq 1–4) indicates a significant dependence on both substituent polarity (σ_I effect) and the mesomeric parameter (σ_R^0 or $\sigma_{R(BA)}$ effect). It can be seen that a slightly better fit was achieved with the $\sigma_{R(BA)}$ scale.[8]

$$SCS = 0.92\sigma_I + 0.37\sigma_{R(BA)} \quad \text{(benzene; } n = 5\text{; SD/RMS = 3\%)} \quad (1)$$

$$SCS = 0.91\sigma_I + 0.54\sigma_R^0 \quad \text{(benzene; } n = 5\text{; SD/RMS = 6\%)} \quad (2)$$

$$SCS = 0.67\sigma_I + 0.29\sigma_{R(BA)} \quad \text{(DMF; } n = 5\text{; SD/RMS = 7\%)} \quad (3)$$

$$SCS = 0.66\sigma_I + 0.42\sigma_R^0 \quad \text{(DMF; } n = 5\text{; SD/RMS = 14\%)} \quad (4)$$

The DSP analysis also indicates that the less positive SCS values in DMF compared to those in benzene for NO_2, CN, F, and Br (Table I) have their origin in both terms; however, the effect is more pronounced for the substituent polarity function ($\rho_I\sigma_I$). We believe that the attenuation of the primary field effect as a result of a greater effective dielectric constant in the polar solvent (DMF) is primarily responsible for the solvent effects observed for NO_2, CN, F, and Br.[9,10] However, the more negative SCS for NH_2 in DMF compared to that in benzene is probably the consequence of an enhanced σ_R value for this substituent due to specific substituent–solvent interactions in the former solvent.

Table I. ^{19}F SCS for Some 1-Fluoro-4-Para-Substituted Phenylbicyclo[2.2.2]octanes (III)

Substituent	SCS,[a,b] ppm Benzene	DMF
NO_2	+0.65	+0.47
CN	+0.58	+0.39
F	+0.28	+0.21
Br	+0.34	+0.28
NH_2	−0.18	−0.31
NH_3^+	+1.93[c]	

[a] Relative to 1-fluoro-4-phenylbicyclo[2.2.2]octane: δ (internal $FCCl_3$) +152.77 ppm (CCl_4); δ (external $FCCl_3$) +150.35 ppm (CCl_4). [b] A positive sign denotes shielding. [c] Solvent CF_3CO_2H.

It is of interest to note that on the basis that the substituent parameters for NH_3^+ in CF_3CO_2H are $\sigma_I = 1.08$ and $\sigma_R^0 = -0.26$,[11] and by utilizing the DSP correlative equation for system III in DMF (eq 4), the calculated SCS for this monopole in system III is approximately +0.6 ppm. In this light, the relatively large upfield SCS (+1.93 ppm) observed for $NH_3^+(CF_3CO_2H)$ in III (Table I) is somewhat perplexing. We believe that part of the problem associated with this charged +F−M substituent is that unlike the groups employed in the correlative analysis (NO_2, CN, F, Br, and NH_2), the induced charges in the phenyl π system due to this group are determined mainly by substituent polarity (σ_I), not mesomerism (σ_R).[12] Thus, contrary to expectations derived from the DSP equations, the secondary field effect emanating from the charges in the π system for NH_3^+ actually reinforces the primary field.

Thirdly, the results for system III (Table I), together with the previously reported *negative* ^{19}F SCS for system II, strongly suggest that two opposing factors (deshielding and shielding contributions) control the response of ^{19}F chemical shifts to an applied electric field and that, moreover, their relative importance is markedly determined by the electronic structure of the chemical bonds in the immediate vicinity of the fluorine atom. Various formulations of ^{19}F NMR shifts in terms of localized bond parameters[1,13] suggest that these two factors can probably be identified with charge density and bond order terms associated with the CF bond. Both terms are important but strongly opposed in these formulations. It should be noted that Stock and Anderson[1] have already proposed the idea that changes in bond order resulting from the interaction between the nonbonding orbitals of the fluorine atom and the endocyclic carbon–carbon bond orbitals may be responsible for some unusual ^{19}F chemical shift trends for unsubstituted bicyclic tertiary fluorides.[14] Interestingly, application of Pople's CNDO/2 method to some 4-substituted bicyclo[2.2.2]octyl-1-fluorides (system I) indicates that although substituents perturb the charge density of the $2p_y$ (σ) orbital, and this appears to correspond well to the σ_I scale, the charge density for both the $2p_z$ and $2p_x$ orbitals remains unchanged, i.e., no π-electronic effects on the fluorine are indicated.[15]

Finally, although the limits of expectation for estimating electric-field contributions are not good owing to uncertainties associated with the distance and effective dielectric constant terms, it is of value to note the crude estimates for COOEt ($\sigma_I = 0.30$)[4] and F ($\sigma_I = 0.50$)[4] in system I based on the polar effect contribution ($\rho_I\sigma_I$) for system III (eq 1) and some simple distance dependency laws (r^{-2} and r^{-3})[5b,16] that have been indicated for electric-field induced chemical shifts. The calculated values are as follows:[17] COOEt = +1.10 ppm (r^{-2}) and +2.21 ppm (r^{-3}); F = +1.84 ppm (r^{-2}) and +3.68 ppm (r^{-3}). However, the observed ^{19}F SCS for COOEt and F are +4.47

(CCl_4) and +9.23 ppm (CCl_4), respectively.[1] Thus, although electrostatic-field effects contribute significantly to the overall ^{19}F SCS for system I, other factors must also contribute importantly to the overall screening term. This conclusion is strongly supported by the fact that the *phenyl* substituent, a very weak polar substituent ($\sigma_I = 0.10$), induces a substantial upfield shift (2.35 ppm)[18] in system I. While a structural effect (electronic or steric in origin) of the kind proposed by Stock and Anderson[1] is a definite possibility, it should be noted that hyperconjugative transfer of charge involving the bridging bond in bicyclo[2.2.2]octyl systems could also be a possible mechanism for affecting ^{19}F SCS in these systems.[13b,19-21]

Experimental Section

Compounds. 1-Fluoro-4-phenylbicyclo[2.2.2]octane (I, X = Ph). Two methods (A and B) were employed. Method B proved to be superior.

A. 1-Methoxy-4-phenylbicyclo[2.2.2]octane[22] (1.5 g, 0.007 mol) was treated with acetyl fluoride (1.1 g, 0.018 mol) according to the procedure described by Suzuki and Morita.[23] The solid obtained on workup was sublimed to afford a white product (0.6 g, 46%): mp 131–132.5 °C (lit.[24] 132–133 °C); ^1H NMR ($CDCl_3$) δ 1.95 (12 H, m, aliphatic), 7.17 (5 H, broad singlet, aromatic).

B. A solution of 1-hydroxy-4-phenylbicyclo[2.2.2]octane[22] (8 g, 0.04 mol) in pyridine–hydrogen fluoride (60 ml)[25] was stirred overnight at room temperature. The white slurry was poured onto ice and the solid collected by filtration. Sublimation afforded 1-fluoro-4-phenylbicyclo[2.2.2]octane (6.8 g, 84%), mp 131–132.5 °C.

1-Fluoro-4-*p*-fluorophenylbicyclo[2.2.2]octane (III, X = F). 1-Hydroxy-4-*p*-fluorophenylbicyclo[2.2.2]octane[22] (0.49 g, 0.00158 mol) was treated with pyridine/HF as described above for the preparation of I. The solid obtained on workup was sublimed to afford a white product (0.2 g, 50%): mp 87.5–89.5 °C; ^1H NMR ($CDCl_3$) δ 1.88 (12 H, m, aliphatic), 7.1 (4 H, m, aromatic).

Anal. Calcd for $C_{14}H_{16}F_2$: C, 75.7; H, 7.3. Found: C, 75.4; H, 7.4.

1-Fluoro-4-*p*-bromophenylbicyclo[2.2.2]octane (III, X = Br). A solution of bromine in carbon tetrachloride (10 ml, 0.5 M solution) was added with stirring to a slurry of silver trifluoroacetate[26] (1.0 g, 0.054 mol) and I (1.0 g, 0.0049 mol) in CCl_4 (10 ml). The reddish brown color of bromine was discharged instantaneously and after addition was complete (30 min) the heavy precipitate of silver bromide was filtered off and washed with a small amount of ether. The solvent was removed under reduced pressure to yield a residue which was sublimed and recrystallized from methanol to afford a white, microcrystalline solid (1.1 g, 79%): mp 130.5–132 °C; ^1H NMR ($CDCl_3$) δ 1.97 (12 H, m, aliphatic), 7.28 (4 H, m, aromatic).

Anal. Calcd for $C_{14}H_{16}BrF$: C, 59.4; H, 5.7. Found: C, 59.3; H, 5.7.

1-Fluoro-4-*p*-cyanophenylbicyclo[2.2.2]octane (III, X = CN) was prepared from the above bromo compound (III) in the general manner outlined by Friedman and Shechter[27] for a number of aromatic nitriles. Sublimation of the crude product followed by chromatography on a silica gel column using hexane as the eluent afforded a white solid (0.44 g, 54%): mp 139–140 °C; ^1H NMR ($CDCl_3$) δ 2.0 (12 H, m, aliphatic), 7.5 (4 H, m, aromatic).

Anal. Calcd for $C_{15}H_{16}NF$: C, 78.6; H, 7.0. Found: C, 78.6; H, 7.2.

1-Fluoro-4-*p*-nitrophenylbicyclo[2.2.2]octane (III, X = NO_2). Concentrated nitric acid (1 ml, sp gr 1.42) was added dropwise to a vigorously stirred suspension of I (1.0 g, 0.0049 mol) and acetic anhydride (10 ml) at 0 °C. After addition was complete, the mixture was stirred for 1 h and then water was added. The ight yellow precipitate was collected and recrystallized from methanol to afford white needles (0.8 g, 65%): mp 121.5–123 °C; ^1H NMR ($CDCl_3$) δ 2.03 (12 H, m, aliphatic), 7.47 (2 H, d, aromatic), 8.13 (2 H, d, aromatic).

Anal. Calcd for $C_{14}H_{16}FNO_2$: C, 67.5; H, 6.5. Found: C, 67.4; H, 6.5.

1-Fluoro-4-*p*-aminophenylbicyclo[2.2.2]octane (III, X = NH_2). A suspension of V (0.9 g, 0.0036 mol) in ethanol (50 ml) was reduced with hydrogen (60 psi) over Adams' catalyst (0.05 g). After 1 h the solution was filtered and the solvent evaporated in vacuo. The residue was dissolved in warm methylene chloride and then diluted with warm hexane until precipitation occurred. The white, needle-shaped crystals were collected (0.6 g, 68%) and dried over P_2O_5 in a nitrogen atmosphere as the amine proved to be unstable to air (mp 190 °C dec). An attempt to purify the amine by recrystallization from aqueous methanol afforded an unknown impurity (10% by GLC): ^1H NMR ($CDCl_3$) δ 1.94 (12 H, m, aliphatic), 3.48 (2 H, broad, NH_2), 6.58 (2 H, d, aromatic) 7.07 (2 H, d, aromatic).

Anal. Calcd for $C_{14}H_{18}FN$: C, 76.7; H, 8.3. Found: C, 76.1; H, 8.4.

Spectra. The ^{19}F NMR spectra were obtained at 84.66 MHz on a Bruker WH-90 Fourier transform NMR spectrometer. The proton broad-band decoupled spectra were recorded at 6000 and 600 Hz spectral widths with 16K/8K data points. Probe temperature was 310 K. The spectra were obtained for benzene and DMF solutions containing 5% w/w of the 1-fluoro-4-para-substituted phenylbicyclo[2.2.2]octane and 10% w/w of 1-fluoro-4-phenylbicyclo[2.2.2]octane. The relative chemical shifts are accurate to at least ±1 Hz.

^1H NMR spectra were measured with a Varian A-60 spectrometer. Gas chromatographic analysis was performed on a Varian 1740 gas chromatograph using a 10-ft column of 5% SE-30 on 100/120 Chromosorb W.

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Registry No.—I (X = Ph), 22947-58-6; III (X = F), 60526-63-8; III (X = Br), 60526-64-9; III (X = CN), 60526-65-0; III (X = NO_2), 60526-66-1; III (X = NH_2), 60526-67-2; 1-hydroxy-4-phenylbicyclo[2.2.2]octane, 2001-62-9; pyridine HF, 32001-55-1; 1-hydroxy-4-*p*-fluorophenylbicyclo[2.2.2]octane, 60526-68-3.

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Reversals in Regiospecificity. The Reactivity of Vinylogous Amides toward Bis Electrophiles

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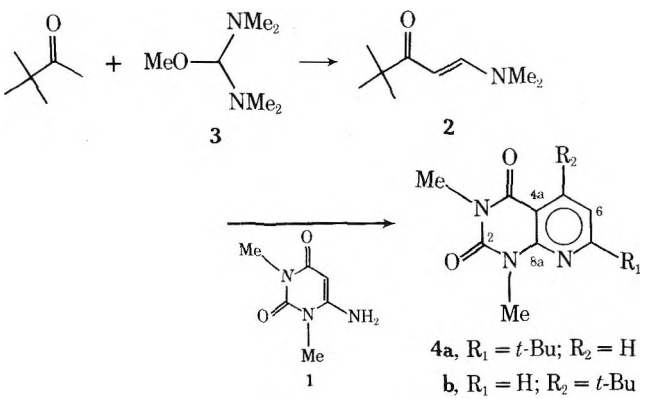
Several examples demonstrating the regiospecific reactivity of vinylogous amides toward bis electrophiles are presented. A reversal in this regiospecificity was accomplished by transformation of the vinylogous amide into the corresponding lithium imide prior to reaction with a bis electrophile.

The regioselective reactivity of primary enamino ketones such as 1,3-dimethyl-6-aminouracil (1) toward both mono and bis electrophiles has been established.[1-11] Furthermore, reversals of this regioselectivity have been accomplished by manipulation of catalyst and solvent.[2,4,10] Accompanying several of these examples were mechanistic proposals based on the difference in reactivity between the primary, exocyclic amino moiety and C-5 toward electrophiles.[1,2,10] The question of reactivity was reduced to one of C- vs. N-alkylation of the vinylogous amide bidentate system.[12]

No cases involving alkylation have been reported in which changes in nucleophilicity of the enamino ketone have resulted *in reversal of regiospecificity.* We wish to report an example of such a reversal and several others confirming the normal regioselective reactivity of enamino ketones.

Reaction of enamino ketone 1 with the tertiary enamino ketone 2, prepared by the aminoformylation of pinacolone with Bredereck reagent 3,[14] regiospecifically afforded only one of the two possible pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **4a** and **4b.**

Scheme I



Compound **4a** would result from an orientation of reactants as depicted in Chart I, whereas **4b** would result from the orientation of Chart II.

The product obtained was assigned structure **4a** based upon a comparison of the product's ^{13}C NMR spectrum with the calculated resonances[15] for structures **4a** and **4b** (Table I), as well as the ^{13}C NMR off-resonance (sfor) carbon–hydrogen spin–spin splitting patterns for C-5 (d) and C-7 (s).

Chart I

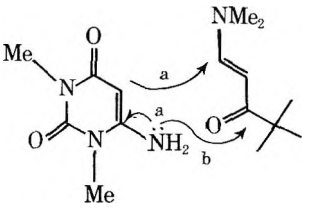
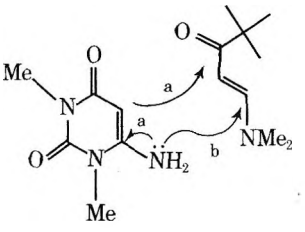


Chart II



Two reaction mechanisms, one involving initial C–C bond formation (pathway a) or one involving as its first step C–N bond formation (pathway b), can be postulated for the formation of **4a.**

There is adequate literature precedent[1,6] for postulating pathway a based on the reactivity of compound 1 toward mono electrophiles. It is to be expected that reaction at nitrogen would be less favorable for vinylogous amides than for enamines owing to the direct electron withdrawal by the carbonyl in the former. Nevertheless, N-acylation of various vinylogous *amide systems has been observed.*[16a]

It was anticipated that a reagent possessing a more significant difference in reactivity between its two electrophilic centers would be useful in providing further proof concerning the reaction mechanism. The reaction of such an electrophile, chlorosulfonyl isocyanate, with compound 1 also afforded a single product.

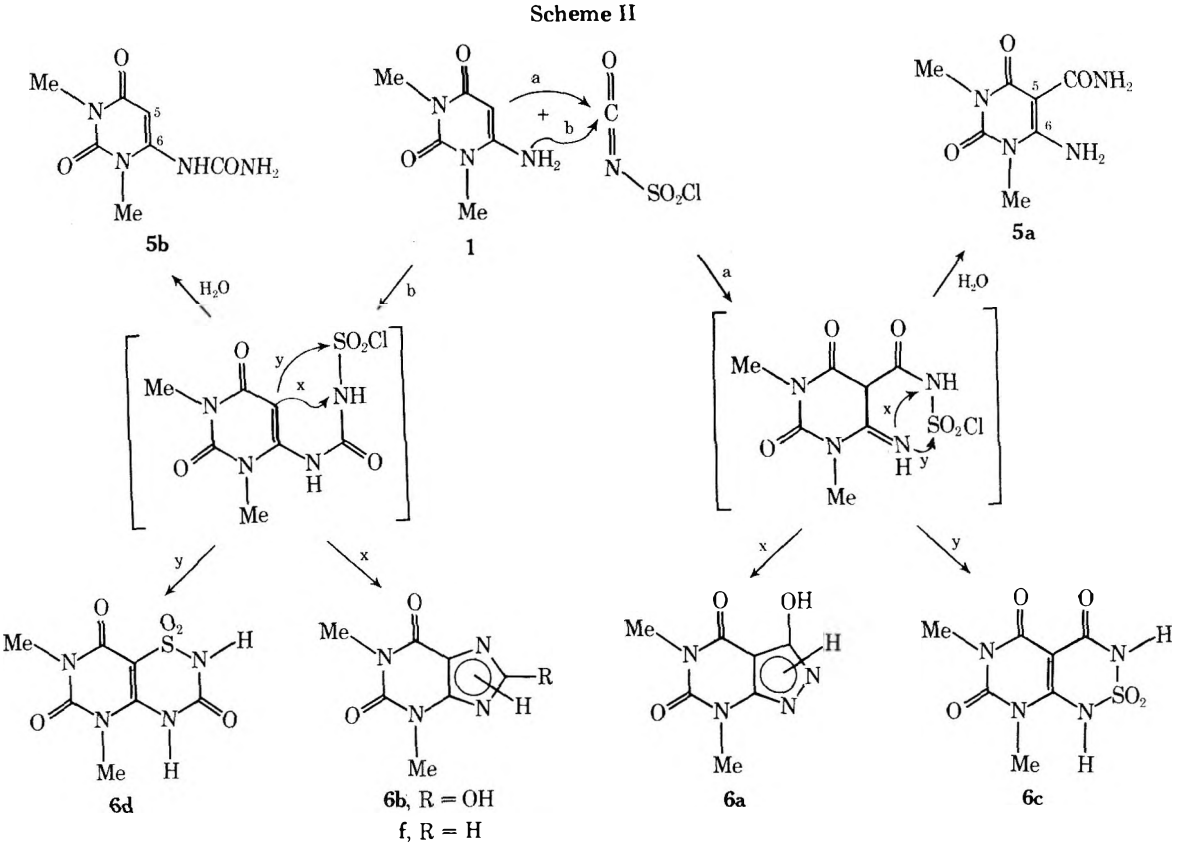
Scheme II depicts the various products that could arise from $ClSO_2NCO$ and 1 via reaction pathways a and b. From these products, **6c** and **6d** could be eliminated on the basis of an elemental analysis. The mass spectrum with a M^+ at *m/e* 198 helped eliminate structures **6a** and **6b** from consideration, but

Table I. Calculated and Observed ^{13}C Absorptions [a]

	4a	4a calcd	4b calcd	5a	6f	12a	12a calcd	12b calcd	12c calcd	12d calcd
N_1CH_3 [b]	28.1	28	28	27.3	27.4					
C_2	150.4	152	152	158.5	151.4	170.9	170	169	160.4	159.4
N_3CH_3 [b]	29.1	36	36	29.4						
C_3						103.2	102	98	106.4	102.6
C_4	151.9	160	161	162.6	154.6	145.8	152	157	149.9	155.2
C_{4a}	108.3	107	107		106.5					
C_5	138.0	135	158	80.5		98.7	103	98	102.1	97.4
C_6	114.7	114	107	149.7	140.3	158.3	158	158	158.8	159.3
C_7	161.5	163	150							
C_{8a} (C_{7a})	175.6	161	161		(148.0)					
t-BuC	38.6	38	38			51.0	51	51	50.9	50.8
									51.0	51.0
t-BuCH_3	30.0	30	30			29.7	30	30	29.7	29.7
Ar$NHCH_3$						28.6	29	29		
-CONHR [c]				170.2		170.9	170	170		
$CONHCH_3$						21.0	21	21		
ArCH_3						26.4	25	25	25.2	25.4
Ar$COCH_3$									33.4	30.8
Ar$COCH_3$									197.5	198.8

[a] Chemical shifts are reported in δ units using Me_4Si as the internal standard. [b] No distinction can be made between the absorption of N_1CH_3 and N_3CH_3. [c] R = H, CH_3.

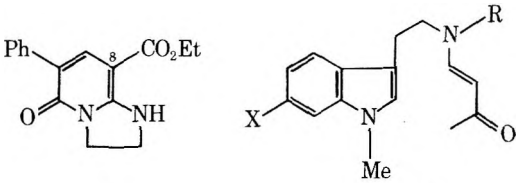
Scheme II



neither it, the high-resolution mass spectrum with a molecular ion at 198.0763 ($C_7H_{10}N_4O_3$), nor the ^1H NMR spectrum, which led us to favor **5a**, could eliminate **5b** as a possibility.

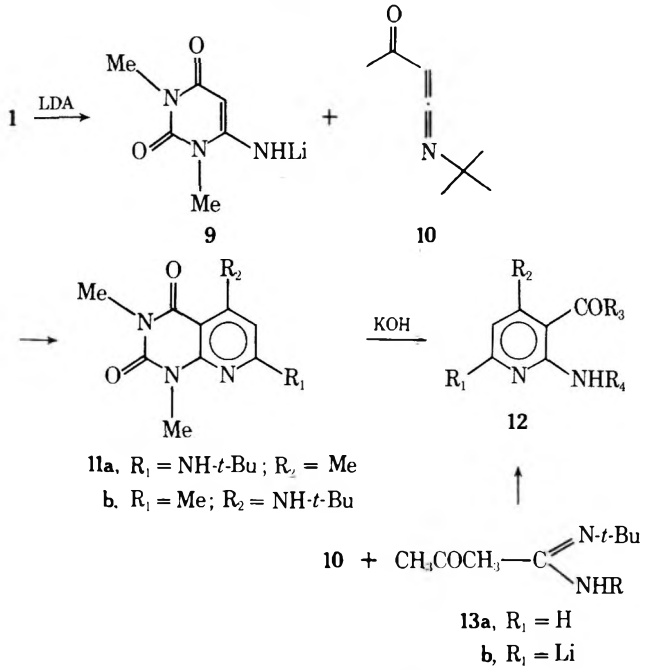
The ^{13}C NMR spectrum (Table I) provided the evidence necessary to assign structure **5a** to the product of the $ClSO_2NCO$ reaction. An unusually high field resonance at 80.5 ppm was assigned to C_5. By comparison, C_8 of compound **7**[17] displayed a resonance at 86.8 ppm. The ^{13}C NMR off-resonance (sfor) carbon–hydrogen spin–spin splitting pattern for C_5 (s) clearly demonstrated a quaternary carbon, thus eliminating **5b** as a possible structure.

The product's structure (**5a**) coupled with the known reactivity[18,19] of $ClSO_2NCO$ toward nucleophiles confirms the reaction mechanism as proposed in the literature,[1,2,10] i.e., initial electrophilic attack at C-5 of compound **1** (pathway a) is probably correct.



Sodium enolates of vinylogous amides are known to undergo both C- and N-methylation.[20] Buchi and co-workers,[21] as part of their elegant syntheses of vindorosine and vindoline, had observed that exposure of **8a** to acetic anhydride led to C-acylation, whereas treatment of the sodium salt **8b** with acetyl chloride provided the *N*-acyl derivative **8c.** It was, therefore, expected that such a manipulation of compound **1** might alter its regioselective reactivity in that initial electrophilic attack of **1** would be on nitrogen and not at C-5. Exposure of vinylogous lithium imide **9,** formed by the treatment of **1** with lithium diisopropylamide (LDA), to *N-tert*-butylacetylketenimine (**10**)[22] provided only one of the two possible regioisomers **11a** or **11b** (Scheme III). Compound **11a** would

Scheme III



	R_1	R_2	R_3	R_4
12a	NH-*t*-Bu	Me	NHMe	Me
b	Me	NH-*t*-Bu	NHMe	Me
c	NH-*t*-Bu	Me	Me	*t*-Bu
d	Me	NH-*t*-Bu	Me	*t*-Bu

result from an orientation of reactants as depicted in Chart III whereas **11b** would result from the Chart IV orientation.

Chart III

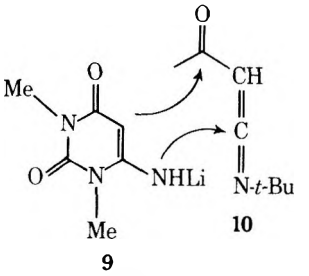
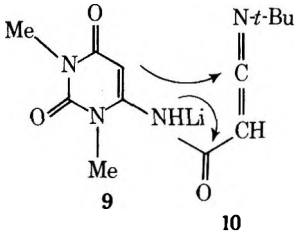


Chart IV



Because of solubility problems, this substance was converted by alkaline hydrolysis into the corresponding diaminonicotinamide **12.** After a comparison of the measured and calculated ^{13}C NMR spectra (Table I), structure **12a** was tentatively assigned to this product.

The calculated ^{13}C NMR resonances of **12a** and **12b** were derived from the ^{13}C NMR spectra of compounds **12c,** whose structure had been determined by x-ray analysis,[23] and **12d.** The syntheses and structure determinations of compounds **12c** and **12d** will be discussed in greater detail later in this publication.

There is adequate literature precedent involving the reactivity of ketenimines[24] as electrophiles to postulate a mechanism involving initial electrophilic attack of the ketenimine on the amide N followed by electrophilic ring closure at C-5 and dehydration.

Such a mechanism would represent a total reversal in the regioselectivity previously demonstrated by compound **1,** wherein initial electrophilic attack was at C-5, and represents the first such reported reversal resulting from a change in the nucleophilicity of the bis nucleophile.

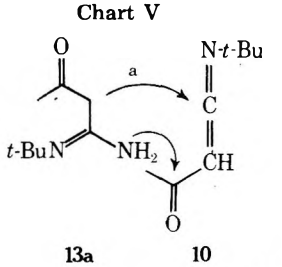
Exposure of aminouracil **1** to kentenimine **10** under neutral conditions, a reaction which should have provided **12b,** led only to products resulting from the decomposition of **10.**

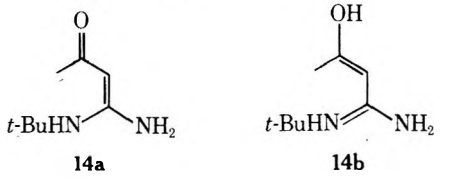
The reaction of lithium amide **9** with bis electrophile **2** was equally disappointing. Less than a 3% yield[25] of the anticipated product **4b** was realized. In addition to starting materials (>80%), a 13% yield of **4a** was also isolated from the product mixture.

Still lacking an example of reversal in regioselectivity in which each of the two possible products from a bis nucleophile and bis electrophile was prepared in turn and in good yield, we next turned to the reactions of ketenimine **10** and amidine **13.**[26] Under neutral conditions (**13a** + **10**), a single product, **12c** or **12d,** was formed in 70% yield. Exposure of **10** to lithium salt **13b** led to a single but different product, again either **12c** or **12d** in 67% yield. Addition of LiBr to the former reaction had no effect on either product composition or yield. Based on ^1H and ^{13}C NMR, IR, UV, and MS data, structures **12c** or **12d** could be assigned to these products but one could not with confidence assign structure **12c** to one and **12d** to the other. An x-ray analysis[23] allowed the assignment of structure **12c** to the product resulting from exposure of ketenimine **10** to lithium amide **13b.** Structure **12d** could, then, by analogy, be assigned to the product resulting from the reaction of **10** with amidine **13a** under neutral conditions.[27] The actual tautomeric forms of **12c** and **12d** in solution cannot be assigned based on the analytical data.

Again, based on the fact that acylketenimines undergo initial nucleophilic attack (a) at the sp carbon, compound **12d** would result from an orientation of reactants as depicted in Chart V. This would require the tautomerization of **13a** into

Chart V

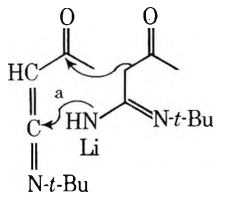




a form such that the methylene carbon might become more nucleophilic, e.g., **14a** or **14b.**

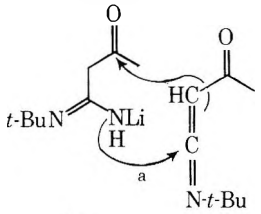
Either the orientation in Chart VI or that in Chart VII would lead to compound **12c.** With both, initial nucleophilic

Chart VI



10 **13b**

Chart VII



13b **10**

attack on the ketenimine (**10**) must be made by the amide nitrogen. These reactions thus represent a clear reversal in regioselectivity of a bis nucleophile toward a bis electrophile due to changes in the former's nucleophilic character.

With the exception of starting materials and their degradation products, no compounds other than those described above could be isolated from the reaction mixtures.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer Model 257 or 457 grating spectrophotometer and NMR spectra were recorded using either a Varian T-60 or EM-360 spectrometer. ^{13}C NMR spectra were recorded using a Varian XLFT-100 spectrometer. Chemical shifts (δ) are recorded relative to Me_4Si; coupling constants (J) are given in hertz. Mass spectra were recorded using either an LKB 9000 or an AEI MS-30-D5-50 spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaporation.

1-Dimethylaminomethylene-3,3-dimethyl-2-butanone (2). A solution of pinacolone (40.0 g, 0.40 mol) and bis(dimethylamino)-methoxymethane[14c] (80 ml) was heated under N_2 at 110 °C for 18 h. Concentration in vacuo followed by distillation (68–73 °C, 0.1 mm) provided 39.0 g (63%) of a yellow oil which solidified on standing at room temperature and which was used without further purification: NMR ($CDCl_3$) δ 1.15 (s, 9 H), 2.94 (s, 6 H), 5.23 (d, 1 H, J = 12 Hz), and 7.58 (d, 1 H, J = 12 Hz); IR ($CHCl_3$) 1650 cm^{-1}.

Anal. Calcd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.1; H, 10.6; N, 8.5.

1,3-Dimethyl-7-(dimethylethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a). To a solution of 6-amino-1,3-dimethyluracil (15.5 g, 0.10 mol) in 10% aqueous HOAc (3 l.) at room temperature was added dropwise a solution of **2** (15.5 g, 0.10 mol) in absolute EtOH (50 ml). The mixture was heated under N_2 at reflux for 18 h, then cooled and the resulting precipitate removed by filtration and washed several times with H_2O. The crude solid was dissolved in Et_2O, and the solution dried and evaporated to give an off-white solid. Recrystallization from a minimum of Et_2O provided 15.0 g (61%) of white crystals: mp 83–85 °C; NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.44 (s, 3 H), 3.70 (s, 3 H), 7.19 (d, 1 H, J = 9 Hz), and 8.31 (d, 1 H, J = 9 Hz); IR ($CHCl_3$) 1710, 1600, 1605, and 1590 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.1; H, 6.9; N, 17.0. Found: C, 63.2; H, 7.3; N, 16.9.

6-Amino-1,3-dimethyl-2,4-dioxo-5-pyrimidinecarboxamide (5a). To a suspension of amino uracil 1 (9.30 g, 0.06 mol) and anhydrous $NaHCO_3$ (5.0 g, 0.06 mol) in CH_2Cl_2 (150 ml) under N_2 was added dropwise a solution of $ClSO_2NCO$ (8.46 g, 0.06 mol) in CH_2Cl_2 (50 ml) and the mixture was stirred at room temperature for 18 h. Water (15 ml) was added and the resulting solids collected and washed with additional H_2O and CH_2Cl_2. Recrystallization from DMF gave 7.94 g (68%) of **5** as a white solid: mp 257.5–259 °C; NMR (Me_2SO) δ 3.15 (s, 3 H), 3.24 (s, 3 H); IR (KBr) 3510, 3310, 1690, and 1640 cm^{-1}; mass spectrum m/e 198.0763 (calcd for $C_7H_{10}N_4O_3$; 198.0753).

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.4; H, 5.1; N, 28.3. Found: C, 42.8; H, 4.9; N, 28.7.

1,3,5-Trimethyl-7-[(dimethylethyl)amino]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11a). A solution of n-BuLi in hexane (25.0 **ml** of 1.6 M, 0.04 mol) was added dropwise to a cooled (20 °C) solution of diisopropylamine (4.04 g, 0.04 mol) in dry HMPA (50 ml). To this red solution under N_2 was added portionwise amino uracil **1** (6.2 g, 0.04 mol) and, after 0.5 h at room temperature, neat *N-tert*-butylacetylketenimine (**10**,[22] 6.20 g, 0.05 mol) was added. After stirring overnight at room temperature, the reaction mixture was stirred into an excess of cold aqueous NH_4Cl. The precipitated solids were collected and dried to give 6.0 g (55%) of the crude product **11a**. Recrystallization from MeOH–$CHCl_3$ gave a white solid: mp 354–356 °C; NMR (CF_3COOD) δ 1.63 (s, 9 H), 2.93 (s, 3 H), 3.38 (s, 3 H), 3.80 (s, 3 H), and 6.92 (s, 1 H).

Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.9; H, 7.3; N, 20.3. Found: C, 60.7; H, 6.9; N, 20.0.

***N*-Methyl-2-(methylamino)-4-methyl-6-[(dimethylethyl)-amino]nicotinamide (12a).** A mixture of dione **11a** (1.00 g, 3.62 mmol) and 40% aqueous KOH (20 ml, 180 mmol) in Me_2SO (50 ml) was heated under N_2 at 130 °C for 4 days. Filtration followed by evaporation of the filtrate gave a residue which was dissolved in H_2O and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated, and the residue chromatographed over silica gel (30:1) affording on $CHCl_3$ elution nicotinamide **12a.** Recrystallization from EtOAc–heptane gave 0.27 g (33%) of needles: mp 172–174 °C; NMR ($CDCl_3$) δ 1.47 (s, 9 H), 2.20 (s, 3 H), 2.87 (s, 3 H), 2.95 (s, 3 H), 5.45 (emergent s, 1 H), 5.40 (broad s, 1 H), and 6.60 (broad s, 1 H); IR ($CHCl_3$), 3440 and 1636 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}N_4O$: C, 62.4; H, 8.9; N, 22.4. Found: C, 62.2; H, 9.2; N, 22.6.

***N'*-*tert*-Butylacetoacetamidine (13a).** To a solution of freshly distilled NH_3 (90 ml) in CH_2Cl_2 (90 ml) at −50 to −60 °C was added a solution of *N-tert*-butyl-5-methylisoxazolinium perchlorate[22] (90 g, 0.375 mol) in CH_2Cl_2 (180 ml). The reaction mixture was allowed to warm to ambient temperature over 12 h, concentrated to 75 ml, and filtered.

The filtrate was washed with saturated K_2CO_3 solution and evaporated to dryness. Recrystallization of the residue from EtOAc gave 49 g (84%) of **13a:** mp 127–129 °C; NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.92 (s, 3 H), 4.58 (broad s, 1.6 H), 5.2 (broad s, 1 H), 7.9 (broad s, 1 H), and 11.03 (broad s, 0.4 H); IR ($CHCl_3$) 3510, 3440, and 1610–1560 cm^{-1}.

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9. Found: C, 61.6; H, 10.7; N, 18.3.

2,4-Di-*tert*-butylamino-3-acetyl-6-methylpyridine (12d). A mixture of amidine **13a** (31.2 g, 0.2 mol) and ketenimine **10**[22] (27.8 g, 0.2 mol) was heated in refluxing THF (200 ml) for 5 h. Evaporation to dryness and crystallization of the residue from MeOH–H_2O provided 38.7 g (70%) of diaminopyridine **12d,** mp 111–114 °C. Recrystallization from heptane gave an analytical sample: mp 115–116 °C; NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.48 (s, 9 H), 2.25 (s, 3 H), 2.48 (s, 3 H), 5.30 (broad s, 1 H), 6.00 (s, 1 H), and 8.06 (braod s, 1 H); IR ($CHCl_3$) 3460, 3260, and 1585 cm^{-1}; UV (MeOH) 2.19 nm (ϵ 22 800), 239 (14 800), and 334 (7450).

Anal. Calcd for $C_{16}H_{27}N_3O$: C, 69.3; H, 9.8; N, 15.2. Found: C, 69.6; H, 10.0; N, 15.2.

2,6-Di-*tert*-butylamino-3-acetyl-4-methylpyridine (12c). To a solution of amidine **13a** (46.8 g, 0.3 mol) in dry THF (600 ml) at 20–40 °C was added a 1.6 M solution of n-BuLi in hexane (192 ml, 0.3 mol) and after stirring at ambient temperature for 1 h a solution of ketenimine **10**[22] (41.7 g, 0.3 mol) in dry THF (200 ml) was added and the stirring was continued for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 ml), and MeOH (500 ml) and Na_2SO_4 (250 g) were added. After the mixture was filtered (Celite) and the filtrate evaporated to dryness, the residue was dissolved in $CHCl_3$ (1 l.), washed with brine, and filtered through silica gel. The product, **12c,** was provided (55.3 g, 67%) by the addition of pentane (200 ml) to the concentrated filtrate: mp 129–131 °C; NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.47 (s, 9 H), 2.32 (s, 3 H), 2.43 (s, 3 H), 4.60 (broad s, 1 H), 5.47 (s, 1 H), and 9.94 (broad s, 1 H); IR ($CHCl_3$) 3440 and 1605–1580 cm^{-1}; UV (MeOH) 222 nm (ϵ 13 650), 267 (15 000), 286 (10 670), and 368 (20 500).

Anal. Calcd for $C_{16}H_{27}N_3O$: C, 69.3; H, 9.8; N, 15.2. Found: C, 69.3; H, 10.2; N, 15.4.

Acknowledgment. The services of the Analytical Section of the Chemistry Department are gratefully acknowledged.

In particular the ^{13}C NMR measurements of Ms. A. D. Kahle, the mass spectral determination of Dr. R. A. Coombs, and the x-ray work of Dr. H. P. Weber, Sandoz, Basle, are appreciated.

Registry No.—**1,** 6642-31-5; **2,** 6135-14-4; **3,** 1186-70-5; **4a,** 60581-88-6; **5a,** 60581-89-7; **6f,** 58-55-9; **10,** 10513-47-0; **11a,** 60581-90-0; **12a,** 60581-91-1; **12c,** 58253-99-9; **12d,** 60581-92-2; **13a,** 60581-93-3; pinacolone, 75-97-8; 6-amino-1,3-dimethyluracil, 6642-31-5; $ClSO_2NCO$, 1189-71-5; *N-tert*-butyl-5-methylisooxazolinium perchlorate, 60581-94-4.

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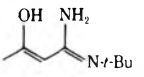
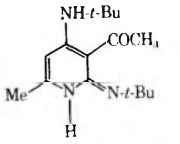
(25) This yield was based on a study of the crude product's ^1H NMR spectrum.
(26) Amidine **13a** exists in solution as a 60:40 equilibrium mixture of **13a** and tautomer i.



i

(27) An isomeric structure, such as ii, cannot be ruled out on the basis of our analytical data.



ii

Determination of Ionization Constants of Alkaloids by Paper Electrophoresis

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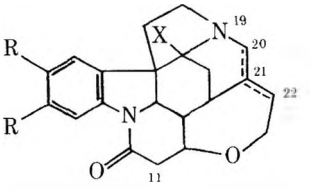
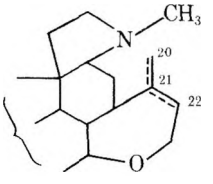
The ionization constants in water of strychnine, brucine, and seven related compounds have been determined by paper electrophoresis using microgram quantities of the bases. Results are in fair agreement with values obtained by potentiometric titration or by changes in solubility as a function of pH.

Arguments based on pK values are often useful in establishing the structures of alkaloids and other natural products.[1] A very simple method for determining pK by paper electrophoresis has been described,[2] but was tested only with fairly simple compounds, all reasonably soluble in water. In this paper we examine the usefulness of this method for strychnine (1), brucine (2), and several related compounds of very limited solubility in water. For such compounds the temptation to determine pK values in mixed aqueous organic solvents is very great but, according to Albert and Serjeant, "should be resisted",[3] because otherwise one loses the advantages accruing from the immense amount of data in the literature for purely aqueous solutions. To check the values obtained by paper electrophoresis, we have also determined the pK values of the bases **1–5** and **7–9** by a solubility method[3] which takes advantage of the limited water solubility of these compounds. The *N*-oxide **6** was sufficiently soluble in water for the conventional potentiometric titration procedure to be used.





1, strychnine: R = X = H; Δ^{21}
2, brucine: R = OMe; X = H; Δ^{21}
3, neostrychnine: R = X = H; Δ^{20}
4, neobrucine: R = OMe; X = H; Δ^{20}
5, pseudostrychnine: R = H; X = OH; Δ^{21}
6, strychnine *N*-oxide: $\geq N^{+19}-\bar{O}$ in place of $\geq N^{19}$
7, benzylidene strychnine: $\geq C^{11}=CHPh$ in place of $\geq C^{11}H_2$
8, base C, Δ^{20}, R = H
9, base D, Δ^{21}, R = H

Table I. Adsorptive Factors of Protonated (ρ_{BH^+}) and Free Bases (ρ_B), and Relative Mobilities (u_r) and Ionization Constants (pK) of Protonated Bases 1–9 in Water

Registry no.	Base	ρ_{BH^+}[a]	ρ_B[b]	u_r Calcd	u_r Exptl	pK PE[c]	pK Solubility[d]
57-24-9	**1**	0.73	0.64	0.55	0.56	8.4	8.41 ± 0.07[f]
357-57-3	**2**	0.66	0.53	0.48	0.46	8.2	8.41 ± 0.05[g]
466-69-3	**3**	0.70	0.63	0.53	0.51	4.5	4.44 ± 0.06
60606-95-3	**4**	0.66	0.58	0.48	0.45	4.5	4.57 ± 0.04
465-62-3	**5**	0.67	0.62	0.51	0.55	6.1	6.13 ± 0.05
7248-28-4	**6**	0.78	0.73	0.58	0.58	3.8	4.13 ± 0.02[e]
25998-70-3	**7**	0.36	0.09	0.24	0.25	*h*	8.38 ± 0.08
14320-69-5	**8**	0.76	0.57	0.56	0.55	7.6	7.54 ± 0.10
30291-05-5	**9**	0.76	0.56	0.56	0.56	7.7	7.24 ± 0.06

[a] From R_f measurements at pH 2.1. [b] From R_f measurements at pH 10.2. [c] By paper electrophoresis. [d] By solubility measurements, except for *e*. [e] Potentiometric titration used. [f] Everett et al.[4] report 8.26 at 25 °C, from titration in dilute solution. [g] Cage[5] reports 8.28 at 25 °C, from titration. [h] Excessive streaking of spots on paper.

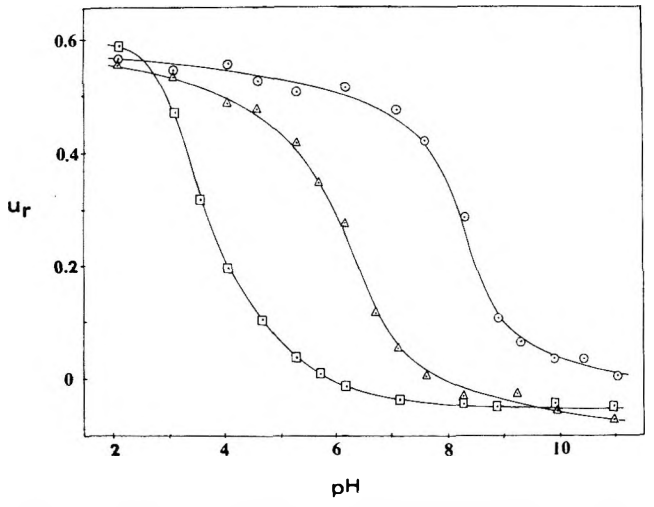


Figure 1. Effect of pH on relative mobilities u_r of strychnine (○), pseudostrychnine (△), and strychnine *N*-oxide (□).

Results and Discussion

The pK values of **1**–**5** and **7**–**9** were determined by following the change of solubility with pH, using ultraviolet absorption as a convenient measure of solubility. These values (Table I) agree fairly well with pK values obtained by potentiometric titration of very dilute solutions, where comparison is possible.[4,5]

The solubility method requires fairly large amounts of material, in contrast to the method of paper electrophoresis, which can be done with less than 100 μg of material if necessary. In the latter method, relative mobilities u_r of the alkaloidal base are plotted against pH. Sigmoid curves are obtained, as shown in Figure 1, and the pH at the inflexion point of the sigmoid curve (found by the graphical method of Stewart and Yates[6]) gives the pK of the protonated base. The pK values thus obtained prove to be in fair agreement with those obtained by the more reliable solubility method, as shown by the comparison in Table I. It should be noted that the pK values obtained by paper electrophoresis are for aqueous solutions at 28.5–30.0 °C (as measured by a thermocouple in contact with the moist paper), depending on the current, and so exact agreement cannot be expected.

The pK values thus determined for compounds **1**, **2**, **3**, and **5**, all tertiary amines, show a linear relationship with the pK^*_{DMC} values for these compounds in 80% dimethyl Cellosolve:[7]

$$pK^*_{DMC} = 0.82\ pK + 0.41 \quad (1)$$

On the other hand, the *N*-oxide **6**, a different type of base, does not obey this relation, nor do the ephedrine-type bases studied by Prelog and Häfliger.[8]

The pK value of strychnine shows it to be about 500 times less basic in water than the bridged tertiary amine quinuclidine;[1] part of this difference may be due to the inductive or field effects of ether and amide groups, part to ring strain.[1] The further decrease in basicity in neostrychnine (**3**) and neobrucine (**4**) has been attributed to increased strain.[1] One might expect then, on naive grounds, an increased basicity for **8** and **9** because of relief of strain.[1] However, models show the protonation (let alone the solvation) of the tertiary amino groups of these compounds to be severely hindered, and they prove to be less basic.

Theoretical Considerations. Some appreciation of the underlying theory[9,10] is desirable if one is devising a procedure for a novel set of acids or bases. Thus for reasonable accuracy the standard ion should be chosen to give $u_r \simeq 1$ when a base is completely protonated. For approximately spherical ions (as in the present case), and in an apparatus where evaporation from the paper is prevented, u_r is given by[9,10]

$$u_r = u/u_{std} = (v_{w(std)}/v_w)^{1/3}(\rho z/\rho_{std} z_{std}) \quad (2)$$

where u and u_{std} are the mobilities of the variably protonated base and of the standard ion, v_w and $v_{w(std)}$ are van der Waals volumes,[11] ρ and ρ_{std} are adsorptive factors measuring retardation by reversible adsorption onto the paper,[10] and z and z_{std} are the charges on the ions.

At pH 2, $z \simeq z_{std} = +1$, $\rho_{std} \simeq 1$, and ρ_{BH^+} (Table I) can be equated (roughly) with the R_f value obtained by ascending chromatography on paper strips. However, in order to obtain the calculated u_r values of the protonated bases BH^+ of Table I, it has been necessary to use the empirical equation

$$u_r = 0.9\rho_{BH^+}(v_{w(std)}/v_w)^{1/3} \quad (3)$$

This may be due to slightly different numerical factors in the Stokes equation for the migration of the protonated alkaloid and the standard ion, because of their very different sizes.[11]

As the pH increases, BH^+ is progressively converted into B, and u_r decreases because of (a) a drop in the net charge z (z_{std} remaining +1)

$$z/z_{std} = [BH^+]/([BH^+] + [B]) = [H^+]/([H^+] + K) \quad (4)$$

and (b) a drop in ρ:

$$\rho = \frac{\rho_{BH^+}[H^+] + \rho_B K}{[H^+] + K} \quad (5)$$

The overall dependence of u_r on pH is given by

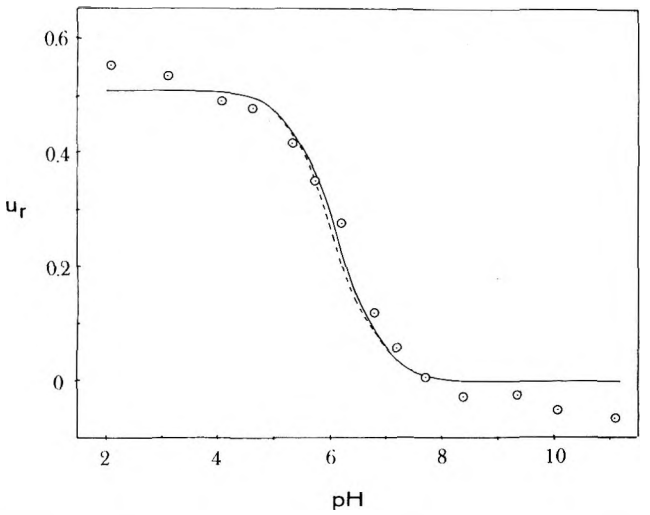


Figure 2. Effect of pH on relative mobility of pseudostrychnine. Points: experimental; broken curve, theoretical for eq 6 with pK = 6.1 and ρ_B, ρ_{BH^+} from Table I; solid curve, theoretical for eq 7.

$$u_r = 0.9\left(\frac{v_{w(std)}}{v_w}\right)^{1/3}\left(\frac{[H^+]}{[H^+]+K}\right)\left(\frac{\rho_{BH^+}[H^+]+\rho_B K}{[H^+]+K}\right) \quad (6)$$

In practice, the change from ρ_{BH^+} to ρ_B is small enough so that it can be ignored, and the last term replaced by ρ_{BH^+}:

$$u_r = 0.9\left(\frac{v_{w(std)}}{v_w}\right)^{1/3}\left(\frac{[H^+]}{[H^+]+K}\right)\rho_{BH^+} \quad (7)$$

This is shown by a comparison of the theoretical curves according to eq 6 and 7 in Figure 2. The agreement of these curves with the experimental points is only approximate, as should be expected in our relatively simple apparatus in which evaporation from the paper is not prevented,[12] and thus the pK values are not as accurate as might be desired. This problem may be overcome by the use of more precisely controlled equipment.

Experimental Section

Materials. Strychnine and brucine were commercial products. Neostrychnine,[13] neobrucine,[13] pseudostrychnine,[14] strychnine *N*-oxide trihydrate,[14] benzylidene strychnine,[15] base C,[16] and base D[16] were prepared according to the literature. A 1% solution of allyltriethylammonium bromide was prepared by reaction of allyl bromide with triethylamine in ethanol–water (4:1); it was not necessary to isolate the salt.

Buffer solutions of ionic strength $\mu \simeq 0.01$ covering the pH range 2–11 were prepared from standard solutions of hydrochloric acid, potassium chloride, potassium acid phthalate, potassium dihydrogen phosphate, sodium hydroxide, and sodium borate.

Paper Electrophoretic Procedure. Strips of Whatman 3 MM chromatography paper 30 cm long and 3 cm wide were placed in the rack of a Beckman Spinco electrophoresis cell (Durrum type) and wetted with buffer solution. After 30 min equilibration in the cell, 10 μl of 1% ethanolic solutions of the following three compounds were spotted on a line pencilled across the midpoint of the strip: the base being investigated; acrylamide, a neutral marker of bulk flow of the buffer solution because of electroendosmosis, evaporation, etc.; and allyltriethylammonium bromide, a standard ion of constant charge +1. A current of 12 mA was passed through the strips for 30 min. They were then removed, partially dried, and sprayed with an acetone solution of potassium permanganate, which revealed transitory yellow spots on purple background (a general test for compounds containing an olefinic double bond). Brucine compounds could also be visualized with a spray of concentrated nitric acid, which showed orange spots on a white background. The spots were outlined with pencil before they faded, and distances measured from the center of the acrylamide spot to the center of the allyltriethylammonium spot (d_{std}), and to the center of the alkaloid spot (d). The relative mobility u_r of the alkaloid is then given by $u_r = d/d_{std}$. Measurements in triplicate were averaged.

Determination of Ionization Constants by Solubility Measurements. The approximate pK of the base was obtained by paper electrophoresis (vide supra). Saturated solutions of the base in several buffer solutions ($\mu \simeq 0.01$) having pH values in the range pH = pK ± 0.8 were then prepared by shaking for 24 h an excess of the solid with 10 ml of buffer solution, kept at 25.0 °C by a thermostat bath. The suspensions were centrifuged, and the pH and absorbance A (at 300 nm for compounds **2**, **4** and **7**, and at 255 nm for all other compounds) of the supernatant solutions were determined. At the same time the absorbance A_B of a solution[17] saturated only with the basic form B of the alkaloid was obtained at a pH = pK + 3. The apparent ionization constant pK' of the conjugate acid BH^+ was obtained as the intercept of the plot of log $[(A/A_B) - 1]$ against −pH, following the equation

$$\log[(A/A_B) - 1] = -\mathrm{pH} + \mathrm{p}K' \quad (8)$$

In water at 25 °C the apparent ionization constant pK' is related to the thermodynamic constant[3] pK by

$$\mathrm{p}K = \mathrm{p}K' - 0.512\sqrt{\mu}/(1 + 1.6\sqrt{\mu}) \quad (9)$$

The difference indicated by the last term in this equation is 0.04, which is within the experimental error of our measurements, and can be neglected.

Acknowledgment. The financial support of the National Research Council of Canada is gratefully acknowledged.

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(17) In separate experiments, it was shown that the absorbance of a given concentration of strychnine is the same at pH 5, when it is in the protonated form BH^+, and at pH 11, when it is in the form of the free base B.

Total Synthesis of (±)-Decamine. A Convenient Scheme for the Synthesis of *cis*- and *trans*-Quinolizidine Alkaloids[1a,b]

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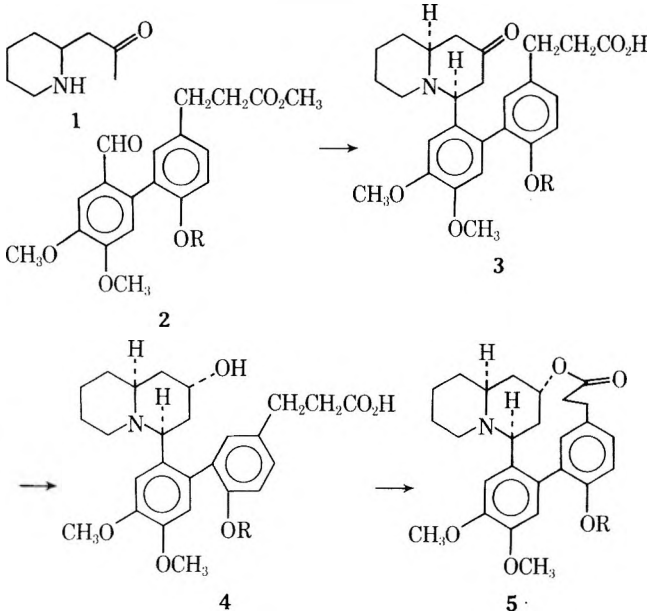
The total synthesis of (±)-decamine, a pentacyclic lythracea alkaloid, is described. The synthesis is based on the stereoselective preparation of *cis*-quinolizidine ketones **6a** and **6b** from isopelletierine and suitably substituted biphenylcarboxaldehydes. Hydrogenation to the thermodynamically less stable α-carbinols was carried out with Pt catalyst in alkaline solution; these were cyclized to the final alkaloids by acid catalysis and in high dilution. A generalized scheme is presented wherein the *cis*-quinolizidine ketone **6a** is epimerized to the trans stereoisomer, thereby acting as precursor to the trans series as well.

Alkaloids from the lythracea family of plants have been known and used in medicine since the early 1600s. Isolation of the first crystalline compounds by Ferris in 1962[2a] resulted in extensive structural studies by Ferris and others[2c,d] that culminated in the recognition, correlation, and classification of over 15 related alkaloids.

Wrobel and Golebiewski[3a] and Hanaoka et al.[3b] independently announced the total synthesis of (±)-decaline, shortly followed by our own report on the total synthesis of racemic methyldecinine[4a] (**5a**) and decinine (**5b**).[4b] Our general synthetic route for the synthesis of these natural products is shown in Scheme I. Base-catalyzed condensation of the pre-

Scheme I

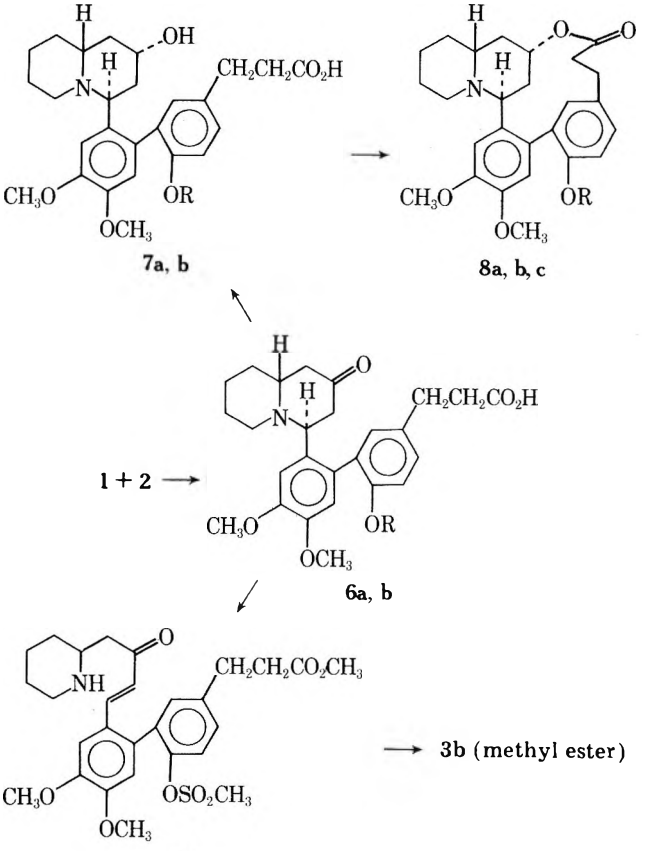


a, R = CH_3
b, R = SO_2CH_3
c, R = H

formed biphenylcarboxaldehydes **2a** and **2b** with isopelletierine gave *trans*-quinolizidine ketone precursors **3a** and **3b**, which were reduced stereoselectively to the desired α-hydroxy acids and cyclized to the desired macrocyclic lactones by high-dilution and acid catalysis. In order to synthesize the related alkaloid decamine, which differs from decinine in the stereochemistry of the quinolizidine moiety only, we had to carry out the alkaline condensation stereoselectively, and under conditions sufficiently mild to prevent the base-induced hydrolysis of the methanesulfonyl protective group in **2b**.

The stereochemistry of the products of the condensation of isopelletierine with aromatic aldehydes depends on the conditions employed. Thus, Matsunaga et al.[5a] obtained a 1:1 mixture of *cis*- and *trans*-quinolizidinones from condensation of **1** with benzaldehyde in aqueous alkaline methanol. In the condensation of **1** with 2-bromoveratraldehyde Hanoaka and co-workers[5b] were able to obtain either the trans product using aqueous methanol or a 3:2 cis:trans mixture by employing aqueous THF for the reaction. In our attempt to obtain *cis*-quinolizidine ketones **6a** and **6b** we examined the effect of temperature and base concentration on the condensation of isopelletierine with biphenylcarboxaldehydes **2a** and **2b** (Scheme II). Predominantly cis product was conveniently obtained at room temperature by the use of weakly alkaline solutions. A mixture of **1** (in the form of its hydrochloride) and **2a** in 30% aqueous ethanol containing 3 equiv of NaOH at room temperature for 5 h gave crystalline keto acid **6a** in 53% yield. The cis stereochemistry about the quinolizidine nucleus was shown by the absence of Bohlmann bands in the solution IR of the methyl ester of **6a** which are present in the IR of the

Scheme II[a]



a, R = CH_3; b, R = SO_2CH_3; c, R = H

[a] See text for reagents.

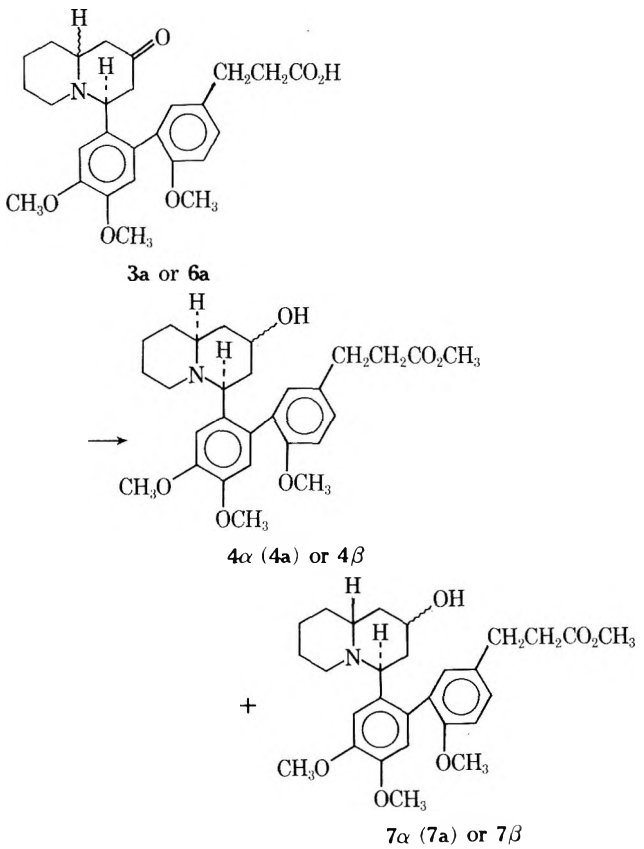
Table I. Reduction Products of Quinolizinones

Starting ketone	Procedure (yield %)	% product distribution 4α	4β	7α	7β
3a	a (85)	88	12		
	b (90)	8	92		
	c (85)	95	5		
6a	a (85)	56	6	32	6
	b (90)			47	53
	c (75)			93	7
6b	c (75)			85 (**7b**)	

methyl ester of **3a** and also by the presence of a broad 1 H signal for the benzylic C_4 methine proton at δ 4.10 ppm,[2a] missing from the NMR of **3a**, probably being buried under the methoxy signals. Similar runs with **1** and **2b** gave keto acid **6b**, in 55% yield, with the expected spectral behavior. An examination of the mother liquors (after diazomethane esterification) indicated about 20–25% starting material **2** that could be recycled in the reaction to increase the combined yields of **6a** and **6b** to 65–70% with less than 10% trans product.

$IrCl_4$ reduction of **6a** and alkaline hydrolysis of the resultant carbinol ester, a previously successful procedure in the methyldecinine synthesis,[4a] resulted in the formation of hydroxy acid **7a**, however, only as the minor component. The major product was the methyl decinine precursor **4a**, arising from an acid-catalyzed epimerization of the cis ketone prior to reduction. To circumvent the difficulty of the purification of diastereoisometric compounds **4a** and **7a** alternative methods for the reduction were needed and examined.

Keto acids **3a** and **6a** were reduced with various agents, and the products were esterified by diazomethane and assayed on



the gas chromatograph (Table I). Reduction of **3a** by $NaBH_4$ gave the thermodynamically more stable β-hydroxy compound (**4β**) in a highly stereoselective manner, whereas the analogous **6a** yielded equal amounts of carbinols **7α** and **7β**. The lessening stereoselectivity in favor of the α carbinol encountered with the $IrCl_4$ reductions in the trans vs. the cis series is contrasted with an improved selectivity using $NaBH_4$. Such effect can be interpreted by assuming that whereas the borohydride delivers its hydride onto the sterically less crowded endo face of the carbonyl in the trans series, the bulky $IrCl_4$ uses this site for complexation and the hydride is transferred to the exo, more crowded surface. The cis compounds are more crowded on the α surface resulting in a partial reversal of the stereochemical outcome of the reductions. Pt–acetic acid hydrogenations resulted in complete recovery of the starting materials; however, Pt in weakly alkaline solutions gave smooth conversion to the desired carbinols **4α** and **7α** with a high degree of stereoselectivity. For characterization, **7α** was converted to and purified as the hydrochloride salt of its the *O*-acetyl methyl ester, whose IR shows the presence of ester groups at 1739 and 1724 cm^{-1} and absence of Bohlmann bands characteristic for the trans system.[6] The NMR of this compound is equally instructive. Besides the signals for the various methoxy groups at δ 4.05, 3.80, and 3.60 [s, (1 + 1 + 2) CH_3O, respectively] and the acetyl group at 2.0 ppm, there is also a broad 1 H signal for the carbinol methine proton at 5.10 ppm ($W_{1/2}$ = 8.0 Hz) fully defining the α-axial configuration. The broad 1 H peak for the C_4 benzylic portion at 4.30 ppm is characteristic of the *cis*-quinolizide ring with an aryl substituent in the 4 position.[2a] The high stereoselectivity of these Pt-catalyzed reductions is surprising in view of the opposite behavior of cyclohexanones under identical conditions. The lone pair of electrons on the nitrogen exerts a very pronounced directive effect about the site of hydrogenation by complexation to the catalyst surface. Such an effect, which favors obtaining the axial alcohols, increases as the media for hydrogenation of quinolizidine ketones is changed from acidic to neutral solutions as shown by Aaron et al.[7] in our instance; in alkaline solutions the effect is multifold.

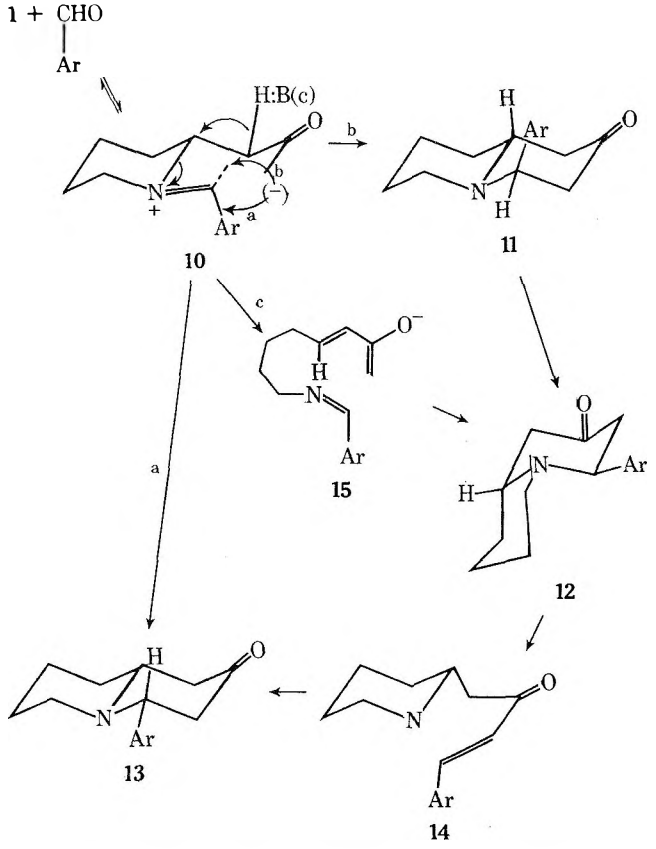
Employing high dilution and *p*-TsOH catalysis cyclization of hydroxy acid **7a** gave (±)-methyldecamine, spectroscopically identical with the methylated natural product. Similar treatment of **7b** yielded the methanesulfonyl derivative of decamine from which **8b** could be easily regenerated by treatment with alcoholic base at room temperature. The product (±)-decamine was identical spectroscopically with natural (−)-decamine. No concurrent hydrolytic opening of the lactone ring was observed during the removal of the methanesulfonyl group.

The successful isolation and purification of cis keto acids **6a** and **6b** enabled us to carry out the total synthesis of decamine and its derivatives economically. The inadvertent acid-catalyzed epimerization of **6b** to **3b** suggested a way to improve on the total synthesis of decinine.[4b] Our previously published synthesis for this compound (Scheme I) suffered from the low yield and difficult purification of trans keto acid **3b**. The yield of trans hydroxy compound **4b**, obtained from the acid-catalyzed epimerization and reduction procedure of **6b** with $IrCl_4$, was already an improvement over our former method; still we wanted to obtain **3b** without the concomitant cis products. We planned to epimerize **6b** by overnight reflux in 1:1 aqueous 3 N HCl–methanol solution, but instead of the expected **3b**, a new product **9** was isolated. The cinnamoyl partial structure was easily deduced for this compound from the NMR spectrum[8a] [AB quartet at δ 7.40 and 6.70 ppm (J_{AB} = 18 Hz)]. The existence of the α,β-unsaturated ketone chromophore could be further seen from bands in the IR (1653 and 1600 cm^{-1}) and UV[8b] (267 and 313 nm) spectra. From this it is apparent that the acid treatment resulted in β-elimination of the tertiary amine giving **9** as product. This unsaturated compound underwent smooth and clean cyclization in 85–90% yield to the trans keto acid ester in refluxing methanol, both supporting the structural assignment and also rendering our epimerization procedure highly successful. The successful

stepwise inverstion of **6b** to **3b** supplies a clue for the overall mechanism of reaction.

Hanaoka and co-workers[9] recently studied the base-catalyzed condensation of **1** with 3-hydroxy- and 3-methoxybenzaldehyde. In aqueous alkaline solutions the 3-methoxy compound gave a 6:1 cis to trans product ratio (**12:13**) whereas the 3-hydroxy analogue yielded trans (**13**) almost exclusively. Carrying out the condensation of 3-methoxybenzaldehyde with **1** in alkaline methanol gave primarily the cis product which slowly epimerized to the thermodynamically more stable trans. The authors proposed that both epimers are formed from the common imminium intermediate **10** (Scheme III). The trans product arises by attack of the incipient

Scheme III



carbanion on the α face of the imminium moiety whereas the cis product is the result of β-attack, as shown by pathways a and b, respectively. Hanaoka also suggested that epimerization of **12** proceeds via the intermediate α,β-unsaturated ketone **14**, though no attempt was made to isolate this material.

Our work strongly supports the idea that the cis quinolizidine is the product of kinetic control. The observation that *trans*-**3b** was obtained selectively from α,β-unsaturated ketone **9** under nonequilibrating conditions lends strong support to the inversion pathway suggested by Hanaoka. We find it more difficult to rationalize the selective formation of the cis adduct by the Hanaoka mechanism. If product development followed the suggested pathway, the trans product would predominate because its transition state is a strain-free pseudochair conformation, while the cis product goes through a more strained pseudoboat transition complex.

An alternative mechanism for the generation of the cis product would suggest the primary formation of the imminium intermediate **10**, which would readily undergo a base-assisted retrograde conjugate addition to obtain acyclic Schiff base intermediate **15**. Its concerted or nonconcerted cycloaddition reaction via the enolate would result in the cis compound selectively, as shown by path c in Scheme III.

One additional observation from the experiments of Hanaoka et al. deserves comment. Strong acid (50% HBr) treatment of the *cis*-quinolizidine **12** (Ar = 3-MeOPh) resulted in demethylation exclusively without inversion to the trans product. Quite analogously, when we reacted **6a** in strong acid (concentrated HCl–MeOH, 1:1) none of the α,β-unsaturated ketone was obtained, and only the dimethoxy ketal of **6a** methyl ester was isolated. These experimental findings lend further support for the overall epimerization pathway; the strongly acidic conditions cause protonation of the carbonyl followed by hydration or ketalization, rather than the proposed β-elimination.

Experimental Section

All melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 spectrometer and signal positions are listed in δ units downfield from Me_4Si as internal standard. Unless indicated otherwise the NMR were determined in ca. 0.01 M $CDCl_3$ solution at ambient temperature. IR spectra were taken on a Perkin-Elmer Infracord in Nujol mulls. Mass spectra were obtained on a Hitachi Perkin-Elmer RMN-6E spectrometer. Spectral data were collected on the analytical samples. Workup in the usual manner implies chloroform extraction followed by washing the extract with brine, drying it over $MgSO_4$, and evaporating the filtrate to obtain the organic product.

Formation of *cis*-Ketoquinolizidines 6a and 6b. Isopelletierine hydrochloride (0.010 mol) was mixed with an equimolar quantity of the biphenylcarboxaldehyde (0.010 mol) in 10 ml of water and 6 ml of ethanol. The mixture was cooled at ice-bath temperature and granular NaOH (0.03 mol) was added. After dissolution of the base the reaction mixture was allowed to stir at ambient temperature for 3.5–5 h. The solution was diluted with water to 50 ml and extracted with chloroform, discarding the organic extract. The alkaline solution was acidified with dilute HCl to pH 2 and was worked up in the usual manner. Trituration with acetone produced crystalline materials. **2a** yielded **6a** (R = CH_3) in 53% yield, mp 193–194 °C.

Anal. Calcd for $C_{27}H_{33}NO_6$·HCl·H_2O: C, 62.12; H, 6.95; N, 2.68. Found: C, 62.01; H, 6.79; N, 2.54.

Biphenylcarboxaldehyde **2b** in the same reaction yielded **6b** (R = CH_3SO_2), 50%, mp 153–155 °C.

Anal. Calcd for $C_{27}H_{33}NO_8S$·HCl·H_2O: C, 55.40; H, 6.15; N, 2.38. Found: C, 55.71; H, 6.00; N, 2.30.

General Reduction Procedures. A. $IrCl_4$ Reductions.[10] The keto acid (0.010 mol) was refluxed with 1.2 g of $IrCl_4$ (or equivalent recovered material) and 28 ml of trimethyl phosphite in a solution of 210 ml of 2-propanol and 70 ml of water for 24–48 h. The solution was concentrated at reduced pressure to approximately 25 ml and diluted to 150 ml with H_2O. After filtering the aqueous solution was extracted with chloroform. Concentration of the aqueous solution to a viscous oil resulted in recovered catalyst that could be used in subsequent reductions. The organic extract was treated in the usual manner to obtain the hydroxy acids, which are at this stage in the form of isopropyl esters. Refluxing with 5% Na_2CO_3 in MeOH–H_2O (1:1) solutions for 5 h quantitatively saponifies the esters to the acids.

B. $NaBH_4$ Reductions. The keto acid (0.001 mol) was dissolved in 15 ml of MeOH, $NaBH_4$ (1.0 g) was added under N_2, and the reaction mixture was stirred overnight at room temperature. The solution was acidified with dilute HCl, diluted with water, and worked up in the usual manner.

C. General Procedure for Catalytic Reductions. The keto acid (0.001 mol) was dissolved in 1 N NaOH and 50 mg of PtO_2 was added; the solutions were hydrogenated in a Parr shaker at 40–50 psi initial hydrogen pressure for 5–8 h. The catalyst was filtered and the alkaline solution was acidified to pH 2 and worked up in the usual manner.

Hydroxy acids obtained by the general procedures were esterified by treatment with diazomethane (methylene chloride solutions, Diazald diazomethane generator procedure) and were acetylated by the acetic anhydride–pyridine method before assays by GLC. Characterization of hydroxy acids (OAc methyl ester unless otherwise noted) was as follows. **4α**: mp 150–150.5 °C; IR 1740, 1724, 1036 cm^{-1}; NMR ($CDCl_3$) δ 8.3 and 6.65 (s, 2 × 1 H), 7.0 (m, 3 H), 5.2 ($W_{1/2}$ = 9.0 Hz, CHOAc), 4.15, 3.85, and 3.65 (s, 4 CH_3O), 2.0 (s, CH_3CO).

Anal. Calcd for $C_{30}H_{39}NO_7$·HCl·0.25H_2O: C, 63.59; H, 7.30; N, 2.44. Found: C, 63.46; H, 7.20; N, 2.47.

4β: mp 224–225.5 °C; IR 1737, 1054, 1043 cm^{-1}; NMR ($CDCl_3$) δ 8.12 and 6.60 (s, 2 × 1 H), 7.05 (m, 3 H), 4.75 ($W_{1/2}$ = 13 Hz,

CHOAc), 4.1, 3.85, 3.75, and 3.60 (s, 4 CH_3O), 2.02 (s, CH_3CO).

Anal. Calcd for $C_{30}H_{39}NO_7$·HCl: C, 64.10; H, 7.17; N, 2.49. Found: C, 64.07; H, 7.04; N, 2.40.

7α: mp 221–222.5 °C; IR 2380, 1739, 1724, 1041 cm^{-1}; NMR ($CDCl_3$) δ 7.95 and 6.60 (s, 2 × 1 H), 7.0 (m, 3 H), 5.10 ($W_{1/2}$ = 8.0 Hz), 4.05, 3.80, and 3.60 (s, 4 CH_3O), 2.0 (s, CH_3CO).

Anal. Calcd for $C_{30}H_{39}NO_7$·HCl·0.25H_2O: C, 63.66; H, 7.05; N, 2.35. Found: C, 63.59; H, 7.02; N, 2.47.

7b (not converted to the acetate): mp 269–270 °C; IR 3333, 2564, 1739, 1342, 1162 cm^{-1}; NMR ($CDCl_3$) δ 7.9 and 6.8 (s, 2 × 1 H), 7.3 (m, 3 H), 4.0 and 3.85 (s, 2 CH_3O), 2.85 (s, CH_3SO_2).

Anal. Calcd for $C_{27}H_{35}NO_8S$·HCl: C, 56.88; H, 6.36; N, 2.46. Found: C, 56.58; H, 6.37; N, 2.53.

Lactonization Experiment. The hydroxy acid **7a** (0.010 mol) was continuously extracted into a benzene solution (4 l.) containing *p*-toluenesulfonic acid (0.4 g); **7b** was extracted into a 1:1 benzene–chloroform solution of *p*-TsOH. After the acids were completely dissolved (4–7 days) reflux was stopped and the solvent was evaporated at reduced pressure. The crude product was worked up in the usual manner to yield a heavy oil which on trituration with ether produced a solid precipitate, mostly polymeric materials. The volume of the ethereal supernatant solution was reduced to approximately 10 ml and the crystallization of the product was initiated by scratching or addition of petroleum ether.

Compound **7a** yielded (±)-methyldecamine (**8a**, mp 197 °C, 40%): *m/e* 451 (P^+), 436 ($P^+ - CH_3$), 420 ($P^+ - CH_3O$), 376 ($P^+ - CH_3O - CO_2$); IR 1715, 1135, 1036 cm^{-1}; NMR ($CDCl_3$) δ 6.9 and 6.8 (s, 2 × 1 H), 7.2–6.8 (m, 3 H), 5.0 ($W_{1/2}$ = 8.0 Hz), 3.9, 3.82, and 3.70 (s 3 CH_3O)

Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.82; H, 7.60; N, 3.14.

Cyclization of **7b** resulted in 35% yield of **8b**: mp 169–171 °C; IR 1727, 1351, 1111, 1052 cm^{-1}; NMR ($CDCl_3$) δ 7.1 and 7.0 (s, 2 × 1 H), 7.3 (m, 3 H), 5.0 ($W_{1/2}$ = 8.0 Hz), 3.90 and 3.85 (s, 2 CH_3O), 3.0 (s, CH_3SO_2).

Anal. Calcd for $C_{27}H_{33}NO_7S$: C, 62.89; H, 6.45; N, 2.72. Found: C, 62.92; H, 6.46; N, 2.73.

Formation of (±)-Decamine (8c). Methanesulfonyl protected **8b** (0.25 g) was stirred in 10 ml of methanol and 5 ml of water with 0.25 g of NaOH for 6 days at ambient temperature. TLC assay showed that starting material was no longer present and a clear solution was obtained. The methanol was evaporated at reduced pressure, and acidification of the solution with dilute HCl resulted in crystalline (±)-decamine (**8c**) hydrochloride, recrystallized from chloroform–ether: mp 312–314 °C (50% yield); *m/e* 437 (P^+), 420 ($P^+ - OH$), 376 ($P^+ - OH - CO_2$); IR 3171, 2564, 1724, 1136, 1123, 1041 cm^{-1}; NMR ($CDCl_3$) δ 8.8 (s, OH), 7.82 and 6.55 (s, 2 × 1 H), 7.0 (m, 3 H), 5.0 ($W_{1/2}$ = 9.0 Hz), 4.55 (br, 1 H), 3.92 and 3.80 (s, 2 CH_3O).

Anal. Calcd for $C_{26}H_{31}NO_5$·HCl·H_2O: C, 63.47; H, 6.96; N, 2.84. Found: C, 63.69; H, 6.61; N, 2.88.

Epimerization of 6a to 3a. The cis keto acid **6a** (0.5 g) was refluxed in 12 ml of N HCl and 12 ml of methanol for 36 h. The solvent was evaporated and the residue was dissolved in chloroform and washed several times with 5% Na_2CO_3 before drying over $MgSO_4$. Evaporation of the organic solvent yielded an oil whose structure was deduced by NMR, IR, and UV (vide supra). Attempted purification by chromatography (GPC or HPLC) resulted in conversion to trans keto acid **3a**. The oil was taken up in 20 ml of methanol and refluxed for 24 h and the solution (a single spot identical with **3a** by TLC) was evaporated to an oil. Spectroscopically this product was found identical with **3a** described previously.[4a]

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Registry No.—1 HCl, 5984-61-2; **2a**, 53937-18-1; **2b**, 57535-51-0; **3a**, 53375-73-8; **4a** α acetate methyl ester HCl, 60633-93-4; **4a** β acetate methyl ester HCl, 60633-94-5; **6a** HCl, 60633-95-6; **6b** HCl, 60633-96-7; **7a**, 60634-00-6; **7a** acetate methyl ester HCl, 60633-97-8; **7b** HCl, 60633-98-9; **8a**, 60686-42-2; **8b**, 60633-99-0; **8c** HCl, 60686-43-3.

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Synthetic Approaches to the Quinolinequinone System of Streptonigrin

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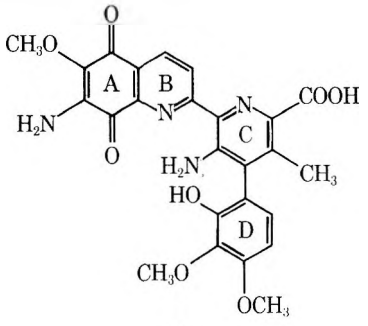
Model studies directed toward synthesis of the quinolinoquinone AB ring system of streptonigrin (1) using approaches based upon Friedlander quinoline synthesis are described. Aldehyde **6** has been prepared from *o*-vanillin, and several unsuccessful attempts were made to convert it to the model quinolinequinone **36**. A successful route to **36** was developed using the *o*-aminobenzaldehyde **30**. Friedlander condensation of **30** with 2-acetylpyridine produced quinoline **31**, which can be transformed in a few simple steps to quinolinequinone **36**. This last route should be applicable to a total synthesis of streptonigrin.

Streptonigrin, a complex antitumor antibiotic isolated[2] from *Streptomyces flocculus*, was shown by chemical studies[3] to have structure **1**. This structure was recently confirmed by



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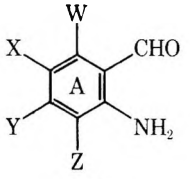
both x-ray analysis[4] and ^{13}C NMR.[5] Streptonigrin shows a broad spectrum of inhibition of several types of tumors,[6] and its mode of action has received considerable attention.[7] Efforts directed toward total synthesis,[8] as well as the synthesis of analogues[9] of the quinolinequinone portion of **1**, have appeared. We are attempting to develop a convergent total synthesis based on the Friedlander condensation of a appropriately substituted 2-acetylpyridine derivative **3** with a



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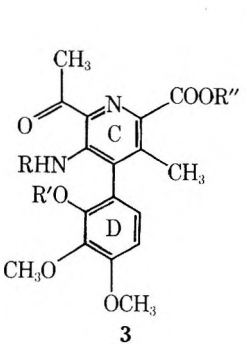

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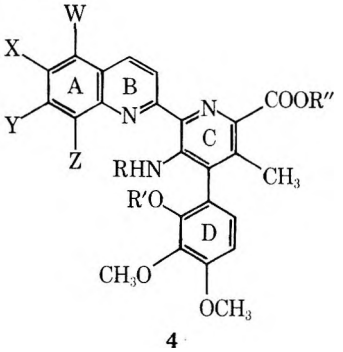

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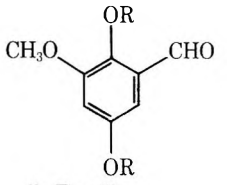
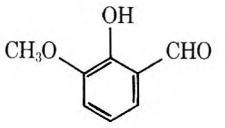
substituted o-aminobenzaldehyde **2** to provide streptonigrin via a quinoline **4**. Using a model series, we have tested such a synthetic strategy.

Initial studies were aimed at the incorporation of as many substituents as possible of the A ring of **1** into the o-aminobenzaldehyde **2**. An appropriate starting material, hydroquinone **5**, can be prepared in 15% yield by potassium persulfate oxidation of o-vanillin (**7**),[10] but a better route to **5** was developed. Fremy's salt oxidation of o-vanillin (**7**) gave no



5, R = H
6, R = $CH_2C_6H_5$



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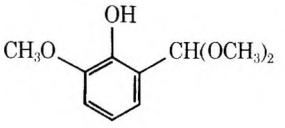

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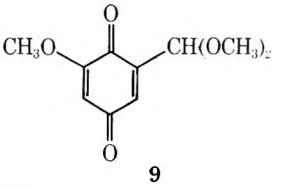

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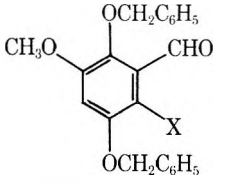
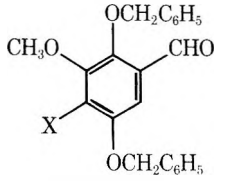
isolable quinone products, but the derived acetal **8** could be oxidized to quinone **9** in 61% yield. However, in view of the inconvenience in preparing and storing large amounts of Fremy's salt, along with the disadvantage of needing large volumes of solvent for this oxidation, an alternate procedure for conversion of **8** to **9** was developed. The oxidation of phenols to quinones using molecular oxygen catalyzed by bis(salicylidene)ethylenediiminocobalt(II) (salcomine) has been reported[11] but has not found wide use in synthesis. Oxidation of **8** in DMF by this method was very clean and produced quinone **9** (91% yield), which could be reduced using sodium hydrosulfite with concomitant hydrolysis of the acetal to give hydroquinone aldehyde **5**. Benzylation of **5** as described afforded the known dibenzyl ether **6**.[12]

Compound **6** was quite reactive toward electrophilic reagents, and upon treatment with cupric nitrate in acetic anhydride gave a single mononitro product, formulated initially as either **10** or **12**. It was not possible at this stage to assign a



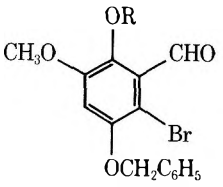
10, X = NO_2
11, X = NH_2



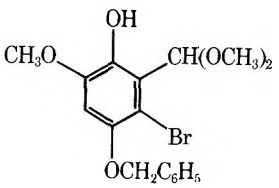
12, X = NO_2
13, X = NH_2

structure to the compound, but either **10** or **12** could be useful in preparing a substituted *o*-aminobenzaldehyde, since it is necessary to eventually introduce nitrogen into both unsubstituted positions of **6**. We were discouraged by the finding that this mononitro compound could not be reduced successfully to the amino aldehyde **11** or **13**.

Bromination of aldehyde **6** was also facile and position selective, but proceeded with some ether cleavage to give a mixture of two monobromo products which were proved to have structures **14** and **15**, respectively. Conversion of **15** to the acetal **16**, followed by oxidation with silver(II) oxide,[13]



14, R = $CH_2C_6H_5$
15, R = H



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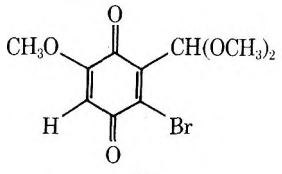

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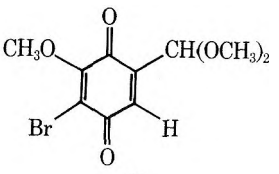

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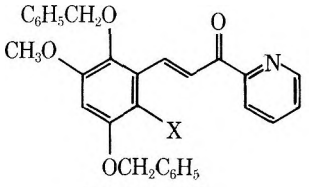
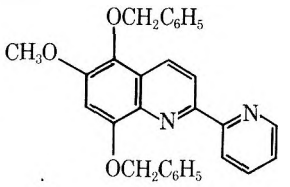
afforded a *p*-quinone which could be assigned structure **17** on the basis of its NMR spectrum. The acetal and vinyl protons in quinone **17** appeared as sharp singlets. In the isomeric quinone **18**, one would expect to observe a coupling between the same two hydrogens.[14] Although conditions could not be found for the bromination which prevented ether cleavage, phenol **15** could easily be rebenzylated to give diether **14**.

By analogy with the bromination product, it was reasonable to assign structure **10** to the mononitration product of aldehyde **6**, and we attempted a modification of the Friedlander synthesis[15] on this nitro aldehyde. Condensation of **10** with 2-acetylpyridine in the presence of sodium hydroxide gave chalcone derivative **19**, but all attempts at reduction of **19** to give pyridylquinoline **21** were unsuccessful.



19, X = NO_2
20, X = Br



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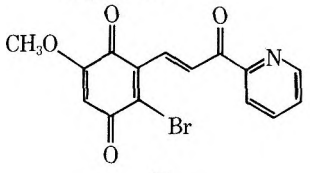

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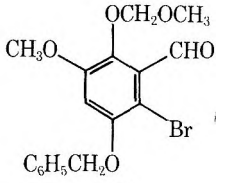

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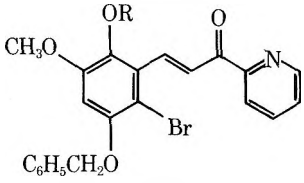
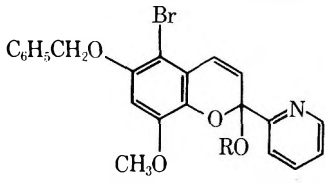
Similarly, bromoaldehyde **14** was condensed with 2-acetylpyridine to give chalcone **20**. We intended to convert this compound to quinone **22**, which on treatment with ammonia might go directly to pyridylquinone **33**. All attempts to remove the benzyl ether protecting groups of **22** to provide the corresponding hydroquinone failed. In an effort to circumvent this problem, hydroxy aldehyde **15** was converted to the methoxymethyl ether **23** and condensed with 2-acetylpyridine to give chalcone **24**. Hydrolysis of the methoxymethyl protecting group with dilute hydrochloric acid gave some of the desired phenol **25**, but primarily yielded the chromene **27**. This mixture of products was acetylated with acetic anhydride in pyridine and separated to afford acetates **26** and **28** in a 1:2 ratio. Although we had hoped to convert phenol **25** to quinone **22**, these difficulties prompted us to seek a different route to the streptonigrin quinolinequinone system.

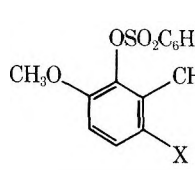


24, R = CH_2OCH_3
25, R = H
26, R = $COCH_3$

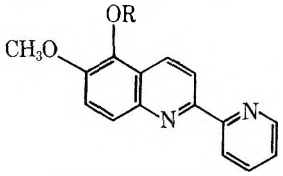


27, R = H
28, R = $COCH_3$

It was decided to use a simpler *o*-aminobenzaldehyde in the Friedlander reaction, and to later introduce the remaining A-ring substituents. The known nitroaldehyde **29**, prepared in two steps from *o*-vanillin (**7**), was reduced as described[16] to *o*-aminoaldehyde **30**. Condensation of this compound with 2-acetylpyridine using Triton B as catalyst gave a 1:4 mixture of pyridylquinolines **31** and **32**, respectively, which was separated by preparative TLC. Sulfonate **31** could be easily saponified to phenol **32**, but, from a preparative viewpoint, it was found easier to combine several steps, and it was possible to go directly from nitroaldehyde **29** to pyridylquinoline **32** without purification of intermediates in 33% overall yield.



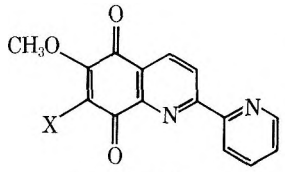
29, X = NO_2
30, X = NH_2



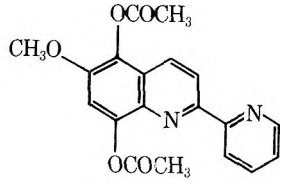
31, R = $SO_2C_6H_5$
32, R = H

Compound **32** could be oxidized to the quinolinequinone **33** by either Fremy's salt[9] or by the salcomine/oxygen procedure. In this case, Fremy's salt was the oxidant of choice, providing quinone **33** in 74% yield, whereas the salcomine/oxygen method gave only a 39% yield of **33**. The structure of **33** was confirmed by hydrogenation to the hydroquinone and acetylation to afford the quinoline diacetate **37**.

Treatment of **33** with chlorine in chloroform at 0 °C provided the chloroquinone **34** (78% yield).[17] Replacement of the chlorine of **34** by azide was a clean reaction, and azidoquinone **35** could be isolated in 88% yield. Reduction of the azide group of **35** with sodium hydrosulfite[18] afforded the purple aminoquinone **36** which had been previously prepared by Rao[9] via a different route.



33, X = H
34, X = Cl
35 X = N_3
36, X = NH_2



37

This last sequence of reactions appears quite promising for constructing the AB system of streptonigrin and we feel that it is also compatible with substituents present in the C and D rings of **1**. Work is now in progress on synthesis of an acetylpyridine such as **3** in order to complete a total synthesis of streptonigrin.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 Infracord spectrometer. NMR spectra were at 60 MHz on Varian A-60A or Perkin-Elmer R-12 spectrometers. Elemental analysis were done by Microtech Laboratories, Skokie, Ill. Merck silica gel 60 was used for column chromatography, and Merck PF_{254} silica gel was used for both analytical and preparative TLC. NMR spectra were determined in deuteriochloroform.

***o*-Vanillin Dimethyl Acetal (8).** A solution of *o*-vanillin (25 g, 0.16 mol), trimethyl orthoformate (120 g, 1.13 mol), and a catalytic amount of *p*-toluenesulfonic acid in absolute methanol was gently refluxed and stirred for 8 h. After removal of solvent, the residue was dissolved in ether, which was washed with brine twice, dried over Na_2SO_4, and

evaporated under reduced pressure. The residue was crystallized from ethyl acetate/hexane to give *o*-vanillin acetal 8 as colorless prisms (25.8 g, 79%): mp 73–74 °C; NMR δ 3.42 (s, 6 H), 3.88 (s, 3 H), 5.67 (s, 1 H), 6.7–7.1 (m, 3 H).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60,59; H, 7.12. Found: C, 60.87; H, 7.19.

2-Dimethoxymethyl-6-methoxy-*p*-benzoquinone (9). A. Oxidation of 8 with Salcomine/Oxygen. To a stirred mixture of *o*-vanillin acetal 8 (5 g, 25.3 mmol) and salcomine[11] (310 mg, 1 mmol) in DMF (40 ml) was introduced oxygen gas for 18 h. The mixture was poured onto crushed ice, and the crystals which precipitated were collected. The mother liquors were extracted with ether, and the organic phase was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crystalline material and the residue from the extraction were combined, the recrystallized from hexane to give the quinone **9** as yellow crystals (5 g, 91%): mp 86–87 °C; IR (Nujol) 1675, 1650 cm^{-1}; NMR δ 3.45 (s, 6 H), 3.87 (s, 3 H), 5.42 (broad s, 1 H), 5.92 (d, J = 2.5 Hz, 1 H), 6.82 (broad d, J = 2.5 Hz, 1 H).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.45; H, 5.71.

B. Oxidation of 8 with Fremy's Salt. A solution of *o*-vanillin acetal 8 (3 g, 15.2 mmol) in methanol (300 ml) was added to a solution of Fremy's salt[19] (13.8 g in 750 ml of 0.05 M KH_2PO_4). The mixture was stirred at room temperature for 2 h and extracted with ether. The ether layer was separated, washed with brine, dried over Na_2SO_4, and evaporated to dryness to give a dark, reddish solid (2 g, 61%). Recrystallization from hexane gave the same yellow quinone as in part A, mp 86–87 °C.

2,5-Dihydroxy-3-methoxybenzaldehyde (5). A solution of quinone **9** (4 g, 18.9 mmol) in ether (100 ml) was added to the solution of $Na_2S_2O_4$ (16 g, 92.0 mmol) in water (100 ml), which was stirred at room temperature for 2 h. The water layer was separated, acidified with concentrated HCl (60 ml), and extracted with ether, which was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from benzene to give the hydroquinone **5** (1.5 g, 47%), mp 142–143 °C. This product was identical with an authentic sample prepared by the method of Merchant et al.[10]

2,5-Dibenzyloxy-3-methoxy-6-nitrobenzaldehyde (10). To a solution of 2,5-dibenzyloxy-3-methoxybenzaldehyde (**6**, 1.4 g, 4 mmol) in acetic anhydride was added cupric nitrate (1.5 g, 8 mmol) and then the solution was heated at 50–65 °C for 15 min. The mixture was poured onto ice, and was extracted with benzene. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel (60 g), which was eluted with benzene/hexane (3/1) to give the nitroaldehyde **10** (0.7 g, 44%). Recrystallization from chloroform/hexane gave pale yellow needles: mp 130–131 °C; IR (Nujol) 1670 cm^{-1}; NMR δ 3.90 (s, 3 H), 5.12 (s, 2 H), 5.19 (s, 2 H), 6.85 (s, 1 H), 7.43 (s, 10 H), 10.16 (s, 1 H).

Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87. Found: C, 67.05; H, 4.77.

2,5-Dibenzyloxy-3-methoxy-6-bromobenzaldehyde (14) and 2-Hydroxy-3-methoxy-5-benzyloxy-6-bromobenzaldehyde (15). To a stirred solution of 2,5-dibenzyloxy-3-methoxybenzaldehyde (**6**, 190 mg, 0.55 mmol) in chloroform (20 ml) was added dropwise a solution of an excess of bromine in chloroform (2 ml) at room temperature. After stirring for 1.5 h, the excess bromine was removed by washing with a solution of sodium bisulfite. The chloroform layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The resulting mixture was separated by preparative TLC using benzene as development solvent to give 2,5-dibenzyloxy-3-methoxy-6-bromobenzaldehyde (**14**, 76.4 mg, 33%) and 2-hydroxy-3-methoxybenzyloxy-6-bromobenzaldehyde (**15**, 83.5 mg, 45%).

14. Recrystallization from ether/hexane gave pale yellow needles: mp 97–98 °C; IR (Nujol) 1680 cm^{-1}; NMR δ 3.85 (s, 3 H), 5.06 (s, 2 H), 5.18 (s, 2 H), 6.82 (s, 1 H), 7.3–7.7 (m, 10 H).

Anal. Calcd for $C_{24}H_{19}O_4Br$: m/e 426.0466. Found: m/e 426.0461.

15. Recrystallization from ether/hexane gave golden yellow needles: mp 86–87 °C; IR (Nujol) 1640 cm^{-1}; NMR δ 3.87 (s, 3 H), 5.17 (s, 2 H), 6.86 (s, 1 H), 7.53 (s, 5 H), 10.50 (s, 1 H).

Anal. Calcd for $C_{15}H_{13}O_4Br$: C, 53.43; H, 3.89. Found: C, 53.38; H, 3.88.

2-Hydroxy-3-methoxy-5-benzyloxy-6-bromobenzaldehyde Dimethly Acetal (16). A mixture of hydroxy aldehyde **15** (83.5 mg, 0.25 mmol), trimethyl orthoformate (1.8 g, 16.98 mmol), and a catalytic amount of *p*-toluenesulfonic acid in absolute methanol (10 ml) was gently refluxed overnight. After removal of solvent, the residue was dissolved in benzene, which was washed with brine, dried over $MgSO_4$, and evaporated to give dimethyl acetal **16** (83.3 mg, 87%). Recrystallization from ether gave pale yellow needles: mp 70–71 °C; NMR δ 3.53 (s, 1 H), 3.84 (s, 3 H), 5.11 (s, 2 H), 5.95 (s, 1 H), 6.67 (s, 1 H), 7.3–7.7 (m, 5 H).

Anal. Calcd for $C_{17}H_{19}O_5Br$: C, 53.28; H, 5.00. Found: C, 53.45; H, 5.11.

2-Dimethoxymethyl-3-bromo-6-methoxy-*p*-benzoquinone (17). A mixture of dimethyl acetal **16** (231 mg, 0.6 mmol), argentic oxide (1.489 g, 12 mmol), and 85% H_3PO_4 (1.5 ml) in dioxane (30 ml) was stirred at room temperature for 1 h.[13] The mixture was filtered, diluted with water, and extracted with ether. The ether layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue was extracted with hexane, which was evaporated and the residue was purified by preparative TLC using benzene/acetone (95/5) as development solvent to give quinone **17.** Recrystallization from hexane gave yellowish-brown crystals (29.1 mg, 16.6%): mp 50–52 °C; IR ($CHCl_3$) 1635, 1650 cm^{-1}; NMR δ 3.53 (s, 6 H), 3.89 (s, 3 H), 5.67 (s, 1 H), 6.18 (s, 1 H).

Preparation of Chalcone 19. To a stirred solution of 2-acetylpyridine (31 mg, 0.26 mmol) in DME (1 ml) and 10% NaOH (1 ml) was added a solution of 2,5-dibenzyloxy-3-methoxy-5-nitrobenzaldehyde (**10**, 80 mg, 0.20 mmol) in DME (5 ml). The solution was stirred at room temperature for 2.5 h, diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC using chloroform/ethyl acetate (9:1) as development solvent to give the chalcone **19** (24.1 mg, 24%). Recrystallization from chloroform/hexane gave pale yellow needles: mp 113–114 °C; IR (Nujol) 1610, 1575, 1520, 1320 cm^{-1}; NMR δ 3.88 (s, 3 H), 4.98 (s, 2 H), 5.21 (s, 2H), 6.67 (s, 1 H), 7.2–8.8 (m, 16 H).

Anal. Calcd for $C_{29}H_{24}N_2O_6$: m/e 496.16530. Found: m/e 496.16343.

Preparation of Chalcone 20. A solution of bromoaldehyde **14** (197.3 mg, 0.46 mmol), 2-acetylpyridine (121 mg, 1 mmol), and 10% NaOH (2 ml) in DME (10 ml) was stirred at room temperature for 18 h. The solution was diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by preparative TLC using benzene/acetone (98/2) as development solvent to give chalcone **20.** Recrystallization from benzene/hexane gave yellow needles (159.2 mg, 67%): mp 127–128 °C; IR (Nujol) 1620, 1580 cm^{-1}; NMR δ 3.85 (s, 3 H), 4.97 (s, 2 H), 5.18 (s, 2 H), 6.70 (s, 1 H), 7.9–8.9 (m, 16 H).

Anal. Calcd for $C_{29}H_{24}NO_4Br$: C, 65.69; H, 4.53. Found: C, 65.38; H, 4.67.

Preparation of Methoxymethyl Ether 23. To a stirred mixture of 50% NaH (220 mg, 4.6 mmol, washed with absolute benzene to remove the mineral oil) and hydroxybenzaldehyde **15** (746.4 mg, 2.2 mmol) in DME (5 ml) was added a solution of excess chloromethyl methyl ether. After stirring for 0.5 h at room temperature, the mixture was basified with 5% NaOH and extracted with benzene. The benzene layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue crystallized from chloroform/hexane as pale yellow needles (667.4 mg, 76%): mp 87–88 °C; IR (Nujol) 1680 cm^{-1}; NMR δ 3.56 (s, 3 H), 3.72 (s, 3 H), 5.12 (s, 2 H), 5.18 (s, 2 H), 6.80 (s 1 H), 7.3–7.7 (m, 5 H), 10.47 (s 1 H).

Anal. Calcd for $C_{17}H_{17}O_5Br$: C, 53.56; H, 4.49. Found: C, 53.65; H, 4.46.

Preparation of Chalcone 24. A solution of bromoaldehyde **23** (667 mg, 1.7 mmol) in DME (15 ml) was added to a solution of 2-acetylpyridine (424 mg, 3.5 mmol) and 10% NaOH (4 ml) in DME (10 ml). The resulting solution was stirred at room temperature for 18 h and extracted with chloroform. The chloroform extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC using chloroform/ethyl acetate (95/5) as development solvent to give chalcone **24,** which was recrystallized from hexane as pale yellow prisms: mp 144–145 °C; NMR δ 3.50 (3 H, s), 7.79 (s, 3 H), 5.04 (s, 2 H), 5.14 (s, 2 H), 6.62 (s, 1 H), 7.3–8.9 (m, 11 H).

Anal. Calcd for $C_{24}H_{22}NO_5Br$: m/e 483.0679. Found: m/e 483.0667.

Chalcone 26 and Chromene 28. A solution of chalcone **24** (196 mg, 0.42 mmol) and 10% HCl (3 ml) in THF (10 ml) was stirred at room temperature for 1 h. The solution was diluted with water and extracted with chloroform. The chloroform extract was washed with brine, dried over Na_2SO_4, and evaporated to afford 151 mg of residue. This crude material was acetylated with acetic anhydride (5 ml) and pyridine (5 ml) to give a mixture of **26** and **28** in a ratio of 1:2. This mixture was separated by preparative TLC using chloroform/ethyl acetate (95/5) as development solvent to give chalcone **26** (48 mg, 24%, R_f 0.40) and chromene **28** (90 mg, 45% R_f 0.24), respectively.

26. Recrystallization from ether gave pale yellow needles: mp 145 °C; IR (Nujol) 1760 cm^{-1}; NMR δ 2.37 (s, 3 H), 3.80 (s, 3 H), 5.17 (s, 2 H), 6.17 (s, 1 H), 8.18 (d, 1 H, J = 6 Hz), 7.3–8.8 (m, 10 H).

Anal. Calcd for $C_{24}H_{20}NO_5Br$: *m/e* 481.0522. Found: *m/e* 481.0498.

28. Recrystallized from ether/hexane: mp 155–157 °C; IR (Nujol) 1750 cm^{-1}; NMR δ 2.37 (s, 3 H), 3.80 (s, 3 H), 5.17 (s, 2 H), 6.17 (s, 1 H), 6.89 (d, 1 H, J = 12 Hz), 7.3–8.9 (m, 10 H).

5-Benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (31) and 5-Hydroxy-6-methoxy-2,2-pyridylquinoline (32). A solution of *o*-nitroaldehyde **29** (336 mg, 1 mmol) in THF was hydrogenated over 5% Pd/C (150 mg).[16] After absorbtion of the theoretical amount of hydrogen, the catalyst was removed and the filtrate was used in the Friedlander condensation immediately. To a stirred solution of 2-acetylpyridine (181 mg, 1.5 mmol) and 10 drops of Triton B was added a solution of the o-aminoaldehyde **30** in THF under a nitrogen atmosphere. The solution was stirred at room temperature for 15 h, diluted with water, neutralized with dilute hydrochloric acid, and extracted with chloroform. The chloroform layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude mixture was purified by preparative TLC using chloroform/methanol (98/2) as development solvent to give 5-benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (**31** 30 mg, 7.6% from nitro aldehyde **29**) and 5-hydroxy-6-methoxy-2,2-pyridylquinoline (**32,** 72 mg, 28.6% from nitro aldehyde **29**).

5-Benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (**31**): mp 93–95 °C (recrystallized from chloroform/hexane); NMR δ 3.71 (s, 3 H), 7.2–8.8 (m, 13 H); λ_{max} (MeOH) 346, 335, 275, 261 nm (log ϵ 4.81, 4.88, 5.37, 5.47).

Anal. Calcd for $C_{21}H_{16}N_2O_4S$: *m/e* 393.08584. Found: *m/e* 393.08643.

5-Hydroxy-6-methoxy-2,2-pyridylquinoline (**32**): mp 184–185 °C (recrystallized from ethanol); NMR δ 3.96 (s, 3 H), 7.39 (d, J = 9 Hz, 1 H), 7.74 (d, J = 9 Hz, 1 H), 7.2–8.7 (m, 6 H); λ_{max} (MeOH) 284, 271 nm (log ϵ 5.49, 5.44).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42, H, 4.79. Found: C, 71.55, H, 4.82.

Hydrolysis of 31 to 32. A stirred mixture of 5-benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (**31,** 121.8 mg, 0.321 mmol) in 15% NaOH (5 ml) and ethanol (5 ml) was refluxed overnight. The mixture was cooled, diluted with water, and neutralized with dilute HCl. The aqueous solution was extracted with chloroform, which was washed with brine, dried over $MgSO_4$, and evaporated to dryness. Recrystallization from ethanol gave pyridylquinoline **32** as pale yellow needles, mp 184–185 °C. This product was identical with a sample prepared above.

Direct Synthesis of 5-Hydroxy-6-methoxy-2,2-pyridylquinoline (32). A stirred solution of *o*-nitroaldehyde **29** (5 g, 14.8 mmol) in THF was hydrogenated over 5% Pd/C (2.5 g).[16] After absorption of the theoretical amount of hydrogen, the mixture was filtered and the filtrate was used in the Friedlander condensation immediately. To a stirred solution of 2-acetylpyridine (2.7 g, 22.3 mmol) and 10 drops of Triton B was added a solution of the aminoaldehyde **30** in THF under an atmosphere of nitrogen. The solution was stirred at room temperature for 15 h, during which additional Triton B was added (10 drops, eight times). The reaction mixture was neutralized with dilute HCl and extracted with chloroform. The chloroform extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. A stirred mixture of the residue and 15% NaOH (100 ml) in ethanol (100 ml) was refluxed overnight. The solution was cooled, diluted with water, and washed with chloroform. The aqueous layer was separated, neutralized with dilute HCl, and extracted with chloroform. The chloroform extract was washed with brine, dried over Na_2SO_4, and evaporated to dryness. Recrystallization from ethanol gave pyridylquinoline **32** as pale yellow needles (1.22 g, 33%).

Preparation of 6-Methoxy-2,2-pyridylquinoline-5,8-dione (33). A solution of pyridylquinoline (**32,** 450 mg, 1.79 mmol) in methanol (250 ml) was added to a stirred solution of Fremy's salt[19] (6.5 g in 250 ml of 0.05 M KH_2PO_4). The solution was stirred for 15 h and diluted with water (500 ml), and the crystalline solid which separated was collected. Recrystallization from benzene/chloroform gave quinolinequinone **33** as yellow needles (350 mg, 74%): mp 260 °C dec; IR (Nujol) 1680, 1610 cm^{-1}; λ_{max} (MeOH) 298, 254 nm (log ϵ 5.44, 5.35); NMR δ 3.98 (s, 3 H), 6.49 (s, 1 H), 8.79 (d, J = 8 Hz, 1 H), 8.88 (d, J = 8 Hz, 1 H), 7.3–8.9 (m, 4 H).

Anal. Calcd for $C_{15}H_{10}N_2O_3$: *m/e* 281.0798. Found: *m/e* 281.0799.

B. Oxidation with Salcomine and Oxygen.[11] Into a stirred mixture of pyridylquinoline (**32,** 73 mg, 0.29 mmol) and salcomine[11] (35 mg, 0.11 mmol) in DMF (20 ml) was bubbled oxygen overnight at room temperature. The mixture was poured onto ice, and was extracted with chloroform. The chloroform layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC using chloroform/methanol (95/5) as development solvent to give quinolinequinone **33** (30 mg, 39%).

5,8-Diacetoxy-6-methoxy-2,2-pyridylquinoline (37). A suspension of 6-methoxy-2,2-pyridylquinoline-5,8-dione (**33,** 83.2 mg, 0.031 mmol) in ethanol (4 ml) and THF (6 ml) was hydrogenated over 5% Pd/$BaSO_4$ (40 mg). After absorption of the theoretical amount of hydrogen, the mixture was filtered, evaporated to dryness, and acetylated with acetic anhydride (5 ml) in pyridine (5 ml). After removal of the solvent, the residue was crystallized from ethanol/chloroform to give colorless needles (92 mg, 84%): mp 199–200 °C; IR (Nujol) 1770, 1750 cm^{-1}; NMR δ 2.50 (s, 3 H), 2.71 (s, 3 H), 4.01 (s, 3 H), 8.32 (d, J = 8.6 Hz, 1 H), 8.73 (d, J = 8.6 Hz, 1 H), 7.3–9.0 (m, 4 H).

Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.71; H, 4.72.

7-Chloro-6-methoxy-2,2-pyridylquinoline-5,8-dione (34). To a stirred cold (0–5 °C) solution of quinolinequinone (**33,** 200 mg, 0.75 mmol) in chloroform (20 ml) was added a solution of ice-cold chloroform saturated with chlorine.[17] The solution was kept at 0–5 °C for 2 h with stirring. The solution was washed with water and dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was recrystallized from chloroform/hexane to give chloroquinolinequinone **34** as small yellow needles (175 mg, 78%): mp 188–191 °C; IR (Nujol) 1660 cm^{-1}; NMR δ 4.35 (s, 3 H), 8.51 (d, J = 8 Hz, 1 H), 8.78 (d, J = 8 Hz, 1 H), 7.3–8.8 (m, 4 H).

Anal. Calcd for $C_{15}H_9N_2O_3Cl$: *m/e* 300.0300. Found: *m/e* 300.0301.

7-Azido-6-methoxy-2,2-pyridylquinoline-5,8-dione (35). To a stirred mixture of 7-chloro-6-methoxy-2,2-pyridyl-5,8-quinolinedione (**34,** 150 mg, 0.5 mmol) in methanol (10 ml) and DMF (10 ml) was added powdered sodium azide at room temperature. After a few minutes, orange crystals began to separate. The stirred mixture was kept at room temperature for 16 h with protection from light. The crystals were collected, washed with 50% methanol, dried over $CaCl_2$ in a vacuum desiccator, and recrystallized from methanol/chloroform to give azidoquinolinequinone **35** as orange needles (143 mg, 88%): mp 137–139 °C; IR (Nujol) 2145, 1660 cm^{-1}; NMR δ 4.30 (s, 3 H), 8.55 (d, J = 8 Hz, 1 H), 8.76 (d, J = 8 Hz, 1 H), 7.3–8.8 (m, 4 H); λ_{max} (MeOH) 310, 279, 250 nm (log ϵ 5.16, 5.07, 5.14).

Anal. Calcd for $C_{15}H_9O_3$: C, 58.63; H, 2.95. Found: C, 58.72; H, 3.11.

7-Amino-6-methoxy-2,2-pyridylquinoline-5,8-dione (36). A stirred mixture of 7-azido-6-methoxy-2,2-pyridylquinoline-5,8-dione (**35,** 76.9 mg, 9.24 mmol) in 50% aqueous methanol (10 ml) was heated with sodium hydrosulfite (150 mg, 0.86 mmol) for 4 h. The mixture was cooled, diluted with water, and extracted with ethyl acetate. Evaporation of the solvent gave a dark, reddish solid which was recrystallized from chloroform/hexane to give 7-amino-6-methoxy-2,2-pyridylquinoline-5,8-dione (**36**) as a purple solid (30 mg, 44%): mp 173–175 °C (lit.[9] mp 172–174 °C); IR ($CHCl_3$) 3370, 3480, 1675, 1630 cm^{-1}; NMR δ 4.12 (s, 3 H), 5.30 (broad s, 2 H, disappeared on D_2O exchange), 8.48 (d, J = 8 Hz, 1 H), 8.78 (d, J = 8 Hz, 1 H), 7.3–8.9 (m, 4 H); λ_{max} (MeOH) 315, 274, 250 nm (log ϵ 5.26, 5.22, 5.43).

Anal. Calcd for $C_{15}H_{11}N_3O_3$: *m/e* 281.0798. Found: *m/e* 281.0799.

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Registry No.—**5,** 2179-22-8; **6,** 2011-05-4; **8,** 60582-30-1; **9,** 60582-31-2; **10,** 60582-32-3; **14,** 60582-33-4; **15,** 60582-34-5; **16,** 60582-35-6; **17,** 60582-36-7; **19,** 60582-37-8; **20,** 60582-38-9; **23,** 60582-39-0; **24,** 60582-40-3; **26,** 60582-41-4; **28,** 60582-42-5; **29,** 2426-60-0; **30,** 60582-43-6; **31,** 60582-44-7; **32,** 60582-45-8; **33,** 60582-46-9; **34,** 60582-47-0; **35,** 60582-48-1; **36,** 57179-31-4; **37,** 60582-49-2; trimethyl orthoformate, 149-73-5; *o*-vanillin, 148-53-8; salcomine, 14167-18-1; Fremy's salt, 14293-70-0; 2-acetylpyridine, 1122-62-9; chloromethyl methyl ether, 107-30-2.

References and Notes

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o-Chloranil–Azlactone Adducts and Their Conversions to Unsaturated Amino Acid Derivatives

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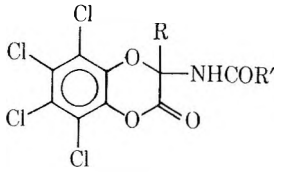
The synthesis of a series of tetrachlorodioxinones (**1**) and their conversions into α-substituted and dehydro amino acid derivatives is discussed. The first synthesis of a dehydro dipeptide derivative from a dipeptide is also reported.

The synthesis of dehydro amino acids and peptides has been of interest to us[2] and to others[3] for some time. In a recent preliminary report,[2c] we described the synthesis of some chlorodioxinones by the reaction of amino acid azlactones with *o*-chloranil. This paper describes that work in more detail and the conversion of the dioxinones into unsaturated amino acid derivatives.

When an acetic anhydride solution of an *N*-benzoyl amino acid was treated with an equimolar amount of o-chloranil at room temperature, the dioxinones (**1**, Table I) crystallized from the solution in 60–95% yields. If the azlactone was formed by treatment of the *N*-acyl amino acid with *N,N'*-dicyclohexylcarbodiimide in an inert solvent, the adducts (**1**) were



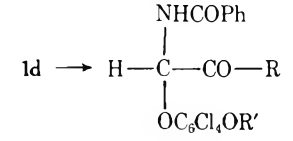
1

a, R = $PhCH_2$; R' = Ph
b, R = $(CH_3)_2CH$; R' = Ph
c, R = CH_3; R' = Ph
d, R = H; R' = Ph
e, R = Ph; R' = Ph
f, R = $(CH_3)_2CHCH_2$; R' = Ph
g, R = $PhCH_2$; R' = CH_3

formed in somewhat lower yields than when acetic anhydride was used. The off-resonance ^{13}C NMR spectra of **1a** and **1d** showed an 88.6-ppm singlet and a 75.2-ppm doublet for C-3 of **1a** and **1d**, respectively. These data along with infrared and ^1H NMR spectra confirmed the dioxinone structure of these compounds.

The chemistry of these compounds was also consistent with the dioxinone structure. They were rapidly converted into α-substituted amino acid derivatives when treated with nucleophiles such as CH_3O^-, $PhNH_2$, and $PhCH_2SH$ and these products are shown in Tables II and III.

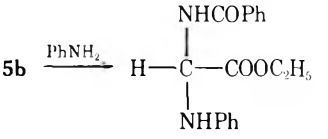
The chemistry of **1d**, formed from *N*-benzoylglycine, was considerably different from that of **1** derived from the other amino acids having an R group larger than hydrogen. The protio compound (**1d**) reacted with water, ethanol, and aniline very rapidly at room temperature giving the α-chlorophenoxy acid salt (**5a**), ester (**5b**), and anilide (**5c**) in excellent yields.



5

a, R = O^-Et_3NH; R' = H
b, R = OEt; R' = H
c, R = NHPh; R' = H
d, R = OEt; R' = CH_3

Since the α-chlorophenoxy group is an excellent leaving group, compounds of the type **5** could be converted into other α-substituted amino acid derivatives as shown below. In this way



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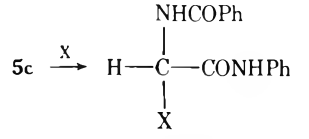
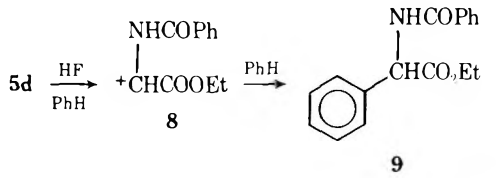


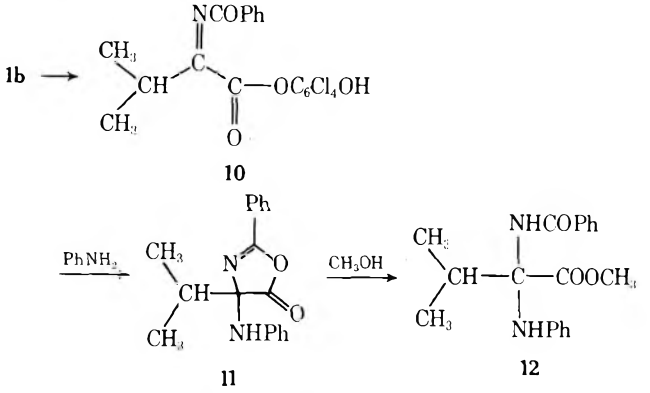
7a, X = CH_3O
b, X = PhNH
c, X = $PhCH_2S$

compounds having *different* groups attached to the α- and carbonyl carbon atoms could be prepared. The ether (**5d**), formed by treatment of **5b** with diazomethane, reacted with anhydrous hydrogen fluoride in benzene solution to give an excellent yield of the known phenylglycine derivative **9**. This



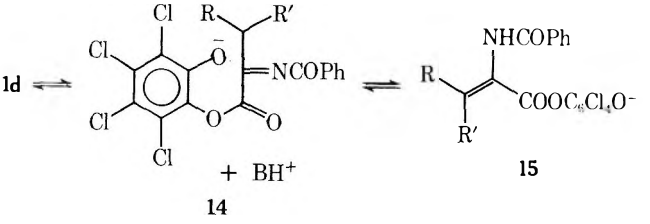
reaction undoubtedly proceeds through an α-carbonium ion (8) as postulated by Ben-Ishai for α-hydroxy-[4a] and α-alkoxyglycine[4b] reactions with nucleophiles under acid conditions.

The dioxinones **1a** (R = $PhCH_2$) and **1b** [R = $(CH_3)_2CH$] did not react with alcohols in the absence of alkoxides, while **1d** (R = H) reacted rapidly. Since **1a** and **1b** have sterically hindered carbonyl groups (trisubstituted α-carbon atom), reaction at this site was very slow. Under basic conditions, however, both **1a** and **1b** reacted rapidly to give α-alkoxy esters. We observed that when **1b** was treated with 1 equiv of aniline, an intermediate having a high-frequency carbonyl absorption at 1825 cm^{-1} was formed. The addition of methanol to this solution converted the intermediate into the α-anilino methyl ester (**12**). These facts are consistent with the formation of an acylimine intermediate (**10**) as a first step. Cyclization to the azlactone **11** by attack of aniline at the azomethine carbon of **10** accounts for the observed high frequency carbonyl absorption. Methanolysis of **11** then finally gives **12**. It was generally found that the dioxinones gave



complex mixtures with a single molar equivalent of amines and that at least 1 more equiv was necessary in order to obtain good yields of α-amino amides (**3**). The liberation of the phenolic hydroxyl group in **10** probably neutralizes part of the amine slowing the reaction, and the liberation of tetrachlorocatechol in the formation of **11** requires at least 1 mol of amine for neutralization.

Since we were interested in the synthesis of dehydro amino acid derivatives, we hoped to convert the quinone adducts into such compounds. The possible equilibrium formation of acylimines (**14**) from **1** using nonnucleophilic bases should[3c]

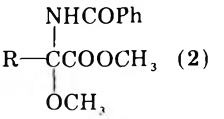


allow their isomerization to the desired α,β-unsaturated compounds (**15**). We felt that O-methylation of **14** would prevent its return to **1** and allow even a slow equilibration to an *O*-methyl-**15** to occur. Consequently, several adducts were treated with methyl iodide/anhydrous potassium carbonate in acetone at room temperature. Instead of a methyl ether of **14** or **15**, the unsaturated acylamino[5] esters (**16a–c**) were isolated in excellent yields along with tetrachlorocatechol

Table I

Compd	Yield, %	Mp, °C	Solvent
1a	73	237–238	Me_2SO
1b	90	200–201	EtOAc–hexane (1:4)
1c	95	228–229	EtOAc–hexane
1d	61	229–230	$CHCl_3$
1e	93	201–203	EtOAc–petroleum ether (1:1)
1f	88	220–221	EtOAc–hexane

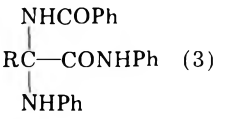
Table II



Compd	Yield, %	Mp, °C	Solvent
2a	77	125–126	EtOH–H_2O(4.5:1)
2b	70	74–75	Et_2O–petroleum ether (3:1)
2d	80	78–80[a]	Et_2O
2e	83	118–119	Et_2O

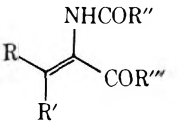
[a] Reference 7, mp 87–88 °C.

Table III



Compd	Yield, %	Mp, °C	Solvent
3a	61	185–187[a]	CH_3OH–H_2O
3b	69	168–169	CH_3OH–H_2O
3d	61	167–168[b]	CH_3OH

[a] **3a** melted at 171–173 °C, resolidified, and remelted as shown. [b] Reference 7, mp 163–164 °C.



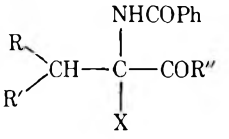
16

a, R = Ph; R′ = H; R″ = CH_3; R‴ = OCH_3
b, R = R′ = CH_3; R″ = Ph; R‴ = OCH_3
c, R = $(CH_3)_2CH$; R′ = H; R″ = Ph; R‴ = OCH_3
d, R = Ph; R′ = H; R″ = Ph; R‴ = OCH_3
e, R = R′ = CH_3; R″ = Ph; R‴ = NHPh

dimethyl ether. The formation of these products from **1** clearly requires the presence of water or methanol in the reaction mixture, since water would convert **15** into the unsaturated acid which would be methylated (esterified) and methanol would afford the ester **16** directly. We took precautions to remove all water from the reaction mixture and, in the light of our experience in the hydrolysis of **1**, we felt that excess water would rapidly convert the intermediate acylimine **14** into an unstable α-hydroxy compound which would decompose spontaneously into the amide and α-keto derivative. In our opinion, the excellent yields of **16** precluded the presence of water. Using NMR spectroscopy, we found that methyl iodide did not react with potassium carbonate in acetone-d_6 over a period of 1 week, but when acetic acid was added both methyl acetate and water were formed in a matter of hours. Apparently, a proton source such as acetic acid or **1** converted potassium carbonate into carbon dioxide and water rather than to potassium bicarbonate as we had expected. The rate

of isomerization, **14** → **15**, was apparently so fast that only **15** was available to react with the water present.

In further work, we found that the α-substituted amino acid derivatives (**17a–c**) underwent elimination in hot pyridine

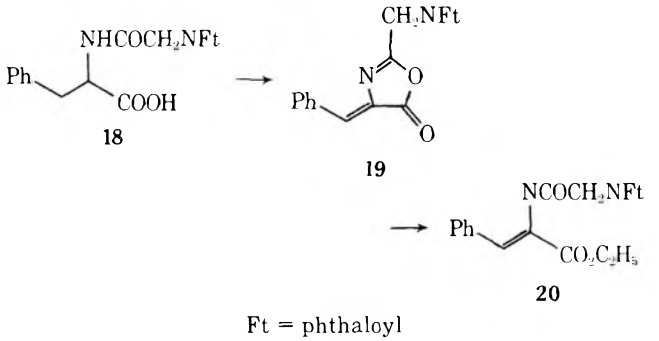


17

a, R = Ph; R′ = H; R″ = OCH_3; X = OCH_3
b, R = R′ = CH_3; R″ = OCH_3; X = OCH_3
c, R = R′ = CH_3; R″ = NHPh; X = NHPh

giving the unsaturated amino acid derivatives (**16b,d,e**). A recent report[3k] by Schmidt describes a similar elimination catalyzed by methoxide ion. Thus, **I** can be converted directly into a dehydro amino acid derivative or through an α-substituted intermediate like **17**.

More interestingly, we were able to prepare an *N*-acyl unsaturated dipeptide directly from the corresponding N-protected saturated compound. When *N*-phthaloylglycyl-DL-phenylalanine (**18**) was treated with *o*-chloranil in acetic anhydride solution, the unsaturated azlactone (**19**) was obtained in 50% yield after recrystallization of the crude precipitate. None of the expected dioxinone adduct was isolated from this reaction. Conversion of **19** into the known[7] ester **20** by ethanolysis confirmed the structure of **19** as drawn. We believe that this is the first report of a direct oxidation of a dipeptide derivative to form a dehydropeptide. We are presently studying the extension of this oxidation procedure to other peptides of biological interest.



18 **19** **20**

Ft = phthaloyl

Experimental Section

General. All melting points were determined on a Nalge Model Y6 micro hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 recording spectrometer with polystyrene as the standard. The ^1H NMR spectra were recorded on a Perkin-Elmer T-60 spectrometer or on a Varian 90-MHz spectrometer with tetramethylsilane as internal standard, and the ^{13}C NMR spectra were determined on a JOEL-PFT-100 spectrometer with Me_4Si as the internal standard; chemical shifts were obtained by computer output. The ultraviolet–visible spectra were determined on a Perkin-Elmer Model 202 spectrophotometer. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga.

General Procedure for the Synthesis of 3-Acylamino 3-Substituted 5,6,7,8-Tetrachloro-1,4-benzodioxin-2(3*H*)-ones (1). A mixture of 20 mmol of *N*-acylamino acid in 20–25 ml of acetic anhydride was warmed until homogeneous and 20 mmol of *o*-chloranil was added. The solution was allowed to stand overnight, cooled in an ice bath, and filtered to give 60–100% yields of the crude crystalline dioxinones (**1**). Recrystallization solvents are given in Table I. The dioxinones all showed the following major IR bands (Nujol): 3230–3370 (N–H), 1765–1805 (C=O), 1655–1670 cm^{-1} (CONH).

Spectra (Off-Resonance) in Me_2SO-d_6. ^{13}C NMR. 1a: 169.9 (s, C=O), 162.0 (s, C=O), 140.8–120.6 (m, C_6H_5), 88.6 (s, CNHCOPh), 45.1 (t, CH_2Ph). **1d:** 167.3 (s, C=O), 159.6 (s, C=O), 143.4–127.7 (m, C_6H_5), 75.2 (d, CHNHCOPh).

3-Acetamido-3-benzyl-5,6,7,8-tetrachloro-1,4-benzodioxin-2(3*H*)-one (1g). A mixture of 8.42 g (34.3 mmol) of o-chloranil and 6.20 g (37.5 mmol) of DL-phenylalanine in 20 ml of acetic anhydride was stirred overnight at room temperature and then cooled at −5 °C for 6 h and filtered, and the solid was dried in vacuo giving 7.35 g (49%) of crude **1a**, mp 224–226 °C dec. Crystallization from ethyl acetate–hexane gave an analytical sample: mp 226–228 °C dec; IR (Nujol) 3250 (NH), 3200 (NH), 1790 (C=O), 1650 (amide C=O), 1540 cm^{-1} (amide II); NMR (Me_2SO-d_6) δ 10.12 (s, 1 H, NH), 7.19 (s, 5 H, C_6H_5), 3.49 (s, 2 H, CH_2). 2.00 ppm (s, 3 H, CH_3).

Anal. Calcd for $C_{17}H_{11}NCl_4O_4$: C, 46.93; H, 2.55; N, 3.22. Found: C, 46.99; H, 2.55; N, 3.31.

General Procedure for Synthesis of *N*-Acyl-α-methoxy Amino Acid Methyl Esters (2). To a methanol suspension of the dioxinone (2–6 mmol) was added 5 ml of 0.5 N $KOCH_3/CH_3OH$ solution and the mixture was stirred magnetically at room temperature until homogeneous (1–16 h, 5 days for **1a**). The solution was evaporated in vacuo and the residue was extracted with methylene chloride. The extracts were washed twice with 5% sodium carbonate solution containing sodium dithionite, dried (anhydrous Na_2SO_4), and evaporated in vacuo to give the crude **2** which was recrystallized. See Table II. Compound **1d** was chromatographed on a silica gel (60–200 mesh) column by elution with $CHCl_3$. The products (**2**) all showed IR (Nujol) bands at 3270–3320 (NH), 1745 (C=O) or 1720–1740, 1765–1770 paired peaks (C=O, **2a** and **2d**), 1650–1675 cm^{-1} (CONH).

General Procedure for Synthesis of *N*-Acyl-α-anilino Amino Acid Amides (3). One millimole of dioxinone was treated with 2–7 mmol of aniline in 50–100 ml of CH_2Cl_2 at room temperature for 16 h. The solution was washed with 2 × 50 ml of 5% sodium carbonate solution containing sodium dithionite, dried (anhydrous Na_2SO_4), and evaporated in vacuo giving the crude crystalline **3** which was recrystallized (Table III). The IR spectra (Nujol) of these products (**3**) showed three bands in the 3290–3440-cm^{-1} region (N–H) and two bands near 1660 and 1695 cm^{-1} (CONH).

Benzyl *N*-Benzoyl-α-benzylmercaptothiolglycinate (4). A solution of 407 mg (1 mmol) of **1d** and 296 mg (2.39 mmol) of benzyl mercaptan in 75 ml of methylene chloride containing 5 drops of triethylamine was stirred for 2 days at room temperature. The reaction mixture was concentrated in vacuo and the crude oil was purified on a column (4.2 × 50 cm) of silica gel (60–200 mesh) by elution with chloroform giving 342 mg (84%) of **4**, mp 106–107 °C. Crystallization from methanol gave an analytical sample: mp 106–107 °C (lit.[7] mp 103–104 °C); IR (Nujol) 3340 (NH), 1690 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.49 (d, 1 H, CHN**H**, J = 8 Hz), 7.68 (m, 5 H, C_6H_5CONH–), 7.26 (s, 10 H, 2 $C_6H_5CH_2$S), 5.83 (d, 1 H, C**H**NH, J = 8 Hz), 4.12 (s, 2 H, SCH_2Ph), 3.94 ppm (s, 2 H, SCH_2Ph).

Triethylammonium *N*-Benzoyl-α-(2-hydroxy-3,4,5,6-tetrachlorophenoxy)glycinate (5a). A solution of 952 mg (2.34 mmol) of **1d** and 20 ml of THF containing 2.34 mmol of H_2O and 2.34 mmol of triethylamine was allowed to stand at room temperature for 6 h. The solvent was evaporated in vacuo, giving 1.25 g of an amorphous solid. Crystallization of the crude solid from ethyl acetate–hexane gave 905 mg (91%) of an analytical sample of **5a:** mp 115–126 °C; IR (Nujol) 3240 and 3190 (NH), 1680 (amide C=O), 1600 cm^{-1} (COO^-); NMR ($CDCl_3$) δ 8.35 (d, 1 H, CHN**H**, J = 8 Hz), 7.81 (m, 2 H, ortho H's of C_6H_5), 7.37 (m, 3 H, meta and para H's of C_6H_5), 5.88 (d, 1 H, NHC**H**, J = 8 Hz), 3.09 (q, 6 H, J = 7 Hz, CH_2CH_3), 1.26 ppm (t, 9 H, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{21}H_{24}N_2O_5Cl_4$: C, 47.93; H, 4.60; N, 5.32. Found: C, 47.80; H, 4.67; N, 5.42.

***N*-Benzoyl-α-(2-hydroxy-3,4,5,6-tetrachlorophenoxy)glycine Ethyl Ester (5b).** A solution of 1.76 g (4.3 mmol) of **1d** in 200 ml of methylene chloride containing 14 ml of ethanol and several drops of acetic acid was stirred at room temperature for 2 h. The reaction was complete when the C=O absorption at 1805 cm^{-1} disappeared. The reaction mixture was evaporated to dryness in vacuo, giving 1.86 g (95%) of crude **5b**, mp 136–142 °C. Crystallization from ethyl acetate–hexane gave an analytical sample: mp 149.5–151 °C dec; IR (Nujol) 3420 (OH), 3320 (NH), 1750 (C=O), 1645 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) δ 9.72 (d, 1 H, CHN**H**, J = 9 Hz), 7.66 (m, 5 H, C_6H_5), 6.37 (d, 1 H, C**H**NH, J = 9 Hz), 4.30 (q, 2 H, CH_2CH_3), 1.27 ppm (t, 3 H, CH_2CH_3).

Anal. Calcd for $C_{17}H_{13}NO_5Cl_4$: C, 45.04; H, 2.89; N, 3.09. Found: C, 45.03; H, 2.92; N, 3.16.

***N*-Benzoyl-α-(2-hydroxy-3,4,5,6-tetrachlorophenoxy)glycine Anilide (5c).** A solution of 507 mg (1.25 mmol) of **1d** and 116 mg (1.25 mmol) of aniline in 125 ml of methylene chloride was stirred at room temperature for 30 min. The reaction was complete when the C=O absorption at 1805 cm^{-1} had disappeared. After the solution was cooled to −5 °C overnight, the precipitate was filtered and dried in vacuo, giving 564 mg (90%) of **5c**, mp 171–172 °C dec. Recrystalliza-

tion from methylene chloride gave an analytical sample: mp 171–172 °C dec; IR (Nujol) 3400 (OH), 3320 and 3270 (NH), 1680 (amide C=O), 1640 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) δ 10.27 (s, 1 H, NHPh), 9.69 (d, 1 H, CHNH, J = 9 Hz), 7.51 (m, 10 H, 2 C_6H_5), 6.51 ppm (d, 1 H; CHNH, J = 9 Hz).

Anal: Calcd for $C_{21}H_{14}N_2O_4Cl_4$: C, 50.43; H, 2.82; N, 5.60. Found: C, 50.33; H, 2.82; N, 5.69.

Ethyl 2-(2,3,4,5-Tetrachloro-5-methoxyphenoxy)-2-benzamidoacetate (5d). A diazomethane (ca. 0.3 g)–ether solution was added to a solution of **5b** (2.27 g) in 20 ml of CH_2Cl_2 at room temperature. After 10 min, the mixture was evaporated in vacuo to give an oil which was crystallized by addition of petroleum ether. The crude product was recrystallized from ether–hexane to afford 1.90 g (81%) of colorless needles: mp 125–127 °C; IR (Nujol) 3200 (NH), 1745 (ester), 1640 cm^{-1} (amide); NMR ($CDCl_3$) δ 7.2–7.8 (m, 6 H, C_6H_5 and NH), 6.64 (d, 1 H, J = 10, CHN), 4.36 (q, 2 H, OCH_2), 3.95 (s, 3 H, OCH_3), 1.35 ppm (t, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{18}H_{15}NO_5Cl_4$: C, 46.28; H, 3.24; N, 3.00. Found: C, 46.10; H, 3.24; N, 3.04.

***N*-Benzoyl-α-anilinoglycine Ethyl Ester (6).** A mixture of 592 mg (1.46 mmol) of **1d**, 6 ml of absolute ethanol, and 2 drops of acetic acid in 100 ml of methylene chloride was stirred at room temperature for 3 h. When the C=O absorption at 1805 cm^{-1} had disappeared, 0.2 ml (2 mmol) of aniline was added. After stirring for 3 days at room temperature, the reaction mixture was washed with two 50-ml portions of 5% sodium carbonate containing sodium dithionite and dried (Na_2SO_4). The solvent was evaporated in vacuo, giving 454 mg of crude yellow **6**. Crystallization from 2:1 ethanol–H_2O gave 283 mg (70%) of **6**, an analytical sample: mp 130–131 °C; IR (Nujol) 3400, 3315 (NH), 1740 (C=O), 1640 (amide C=O), 1610 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 9.20 (d, 1 H, J = 8 Hz, CHNH), 7.84–6.92 (m, 10 H, 2 C_6H_5), 6.12 (d, 1 H, J = 8 Hz, CHNH), 4.18 (q, 2 H, OCH_2CH_3), 1.19 ppm (t, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.59; H, 6.10; N, 9.32.

***N*-Benzoyl-α-methoxyglycine Anilide (7a).** A solution of 867 mg (1.73 mmol) of **5c** in 50 ml of methanol containing 10 ml of 0.5 N potassium methoxide was allowed to stand at room temperature for 1 h. The solvent was evaporated in vacuo, the residue was suspended in 50 ml of methylene chloride, and the mixture was washed with two 50-ml portions of 5% sodium carbonate containing sodium dithionite and was dried (Na_2SO_4). The solvent was evaporated in vacuo, giving 416 mg (86%) of crude **7a**, mp 132.5–134 °C. Crystallization from 1:1 methanol–H_2O gave 400 mg (82%), an analytical sample: mp 134–135 °C (lit.[7] mp 135–136 °C); IR (Nujol) 3330, 3270 (NH), 1695 (amide C=O); NMR (Me_2SO-d_6) δ 9.94 (s, 1 H, PhNHCO), 9.16 (d, 1 H, CHNH, J = 8 Hz), 7.52 (m, 10 H, 2 C_6H_5), 5.68 (d, 1 H, CHNH, J = 8 Hz), 3.43 ppm (s, 3 H, OCH_3); ^{13}C NMR (off-resonance) (Me_2SO-d_6) 167.1 (s, C=O), 165.9 (s, C=O), 138.3–119.8 (m, C_6H_5), 80.2 (d, CH), 55.4 (q, CH_3).

***N*-Benzoyl-α-benzylmercaptoglycine Anilide (7c).** A mixture of 443 mg (0.884 mmol) of **5c** in 50 ml of methylene chloride containing 1.02 mmol of benzyl mercaptan and several drops of triethylamine was stirred at room temperature overnight. The reaction mixture was washed with two 50-ml portions of 5% sodium carbonate containing sodium dithionite and dried (Na_2SO_4), and the solvent was evaporated in vacuo, giving a solid residue. Crystallization from methanol gave 214 mg (64%) of **7c**, mp 197–199.5 °C. Further recrystallization from methanol afforded an analytical sample: mp 200–201 °C; IR (Nujol) 3260 (NH), 1655 (amide C=O), 1635 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) δ 10.38 (s, 1 H, PhNH), 8.92 (d, 1 H, CHNH, J = 8 Hz), 7.50 (m, 15 H, 3 C_6H_5), 5.96 (d, 1 H, CHNH), J = 8 Hz), 4.12 (unsymmetrical doublet, J_{ax} = 18 Hz, SCH_aH_xPh) and 3.98 ppm (unsymmetrical doublet, J_{ax} = 18 Hz, SCH_aH_xPh).

Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.36; N, 7.44. Found: C, 70.07; H, 5.45; N, 7.46.

Ethyl *N*-Benzoylphenylglycinate (9) from 5d. A solution of **5d** (234 mg) in 10 ml of dry benzene was saturated with dry HF at room temperature. After 10 min, the mixture was evaporated in a stream of dry N_2, the residue was dissolved in ether, and the solution was washed with 10% Na_2CO_3 solution. Evaporation of the organic phase gave crystals which were recrystallized from hexane to afford 120 mg (85%) of **9**: mp 87.5–88 °C (lit.[8] mp 89 °C); IR (Nujol) 3350 (NH), 1740 (ester), 1640 cm^{-1} (amide). The basic washing was acidified with HCl to give 100 mg (78%) of tetrachlorocatechol monomethyl ether, mp 121–123 °C (lit.[9] mp 123–124 °C). Hydrolysis of **9** in boiling concentrated HCl for 2 h gave DL-phenylglycine hydrochloride, whose IR was identical with that of an authentic sample.

***N*-Benzoyl-α-anilinovaline Methyl Ester (12).** A solution of 1.19 g (2.65 mmol) of **1b** in 13 ml of methylene chloride containing 7.5 mmol of triethylamine and 2.65 mmol of aniline was allowed to stand at room temperature, and the reaction was followed by TLC and IR. When complete (IR absorption showed a C=O at 1825 cm^{-1}), 1 ml of methanol was added to the solution which was allowed to stand at room temperature for 6 h. After the addition of 50 ml of methylene chloride, the solution was washed with three 50-ml portions of 5% sodium carbonate containing sodium dithionite and dried (Na_2SO_4), and the solvent was evaporated in vacuo, giving a mixture of products. Crystallization from methanol–H_2O gave 323 mg (37%) of crude **12**, mp 141–145 °C. Recrystallization from methanol–H_2O gave 238 mg of an analytical sample of **12**: mp 162.5–164.5 °C; IR (Nujol) 3420, 3440, and 3260 (NH), 3310, 3180 sh (NH), 1745 (C=O), 1640 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 7.70–6.56 (m, 11 H, 2 C_6H_5, NH), 5.13 (broad s, 1 H, NH), 3.83 (s, 3 H, OCH_3), 3.13 [m, 1 H, $(CH_3)_2CH$], 1.17 (d, 3 H, J = 7 Hz, CH_3CH), 0.99 ppm (d, 3 H, J = 7 Hz, CH_3CH).

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.09; H, 6.84; N, 8.62.

Methyl α-Benzamido-β,β-dimethylacrylate (16b). Method A. From 1b. A mixture of 634 mg (1.41 mmol) of **1b**, 500 mg (3.61 mmol) of finely divided anhydrous (dried 150 °C) potassium carbonate, and 0.18 ml (2.9 mmol) of methyl iodide in 8 ml of acetone was stirred at room temperature for 2 days. The reaction mixture was filtered, and the solvent was evaporated in vacuo. The residue was purified by chromatography on a column (4.2 × 75 cm) of silica gel (60–200 mesh) by elution with 1:1 chloroform–hexane giving 331 mg (96%) of tetrachlorocatechol dimethyl ether, mp 92–93 °C, followed by 291 mg (100%) of **16b**, mp 129–130.5 °C. Crystallization from benzene gave 235 mg: mp 129–130.5 °C, resolidified and remelted at 137–138 °C (lit.[10] mp 137–138 °C); IR (Nujol) 3260 (NH), 1720 (C=O), 1640 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 8.13–7.85 (m, 3 H, NHCOPh, ortho H's of C_6H_5), 7.65–7.33 (m, 3 H, meta and para H's of C_6H_5), 3.74 (s, 3 H, OCH_3), 2.18 (s, 3 H, CH_3C=), and 1.88 ppm (s, 3 H, CH_3C=).

Method B. From *N*-Benzoyl-α-methoxyvaline Methyl Ester (17b). A solution of 303 mg (1.14 mmol) of **17b** in 2 ml of pyridine was refluxed for 2 h. The solvent was evaporated in vacuo, and the crude solid was crystallized from benzene, giving 256 mg (96%) of **16b**, mp 136–137 °C, spectrally identical with a sample obtained by method A.

Methyl α-Benzamidocinnamate (16d). A solution of 307 mg (0.98 mmol) of **17a** in 2 ml of pyridine was refluxed for 3 h. The solvent was concentrated in vacuo, and the crude oil residue was purified on a column (4.2 × 30 cm) of silica gel (60–200 mesh). Elution with chloroform gave 180 mg (65%) of crude **16d** which was crystallized from ethanol–H_2O giving 100 mg: mp 137–139 °C (lit.[11] mp 140–141 °C); IR (Nujol) 3330 (NH), 1715 (C=O), 1655 cm^{-1} (amide C=O).

Methyl (*Z*)-α-Benzamido-β-isopropylacrylate (16c). A mixture of 1.19 g (2.57 mmol) of **1f**, 1.5 g (10.8 mmol) of finely divided anhydrous potassium carbonate, and 0.75 ml (12 mmol) of methyl iodide in 6 ml of acetone was stirred at room temperature for 2 days. The reaction mixture was filtered, and the solvent was evaporated in vacuo. The residue was separated on a column (4.2 × 75 cm) of silica gel (60–200 mesh) by elution with 1:1 chloroform–hexane, giving 601 mg (85%) of tetrachlorocatechol dimethyl ether, mp 92–93 °C, and 541 mg (86%) of **16c**, mp 104–108 °C. Crystallization of the crude **16c** from ethyl acetate–hexane gave an analytical sample: mp 111–112 °C; IR (Nujol) 3240 (NH), 1730 and 1720 (C=O), 1660 and 1640 cm^{-1} (amide C=O, C=C); NMR (CD_3COCD_3) δ 8.13 (m, 2 H, ortho H's of C_6H_5), 7.67 (m, 3 H, meta and para H's of C_6H_5), 6.67 [d, 1 H, J = 10 Hz, $(CH_3)_2CHCH$=], 3.76 (s, 3 H, OCH_3), 2.76 [m, 1 H, $(CH_3)_2CH$–], 1.03 ppm [d, 6 H, J = 7 Hz, $(CH_3)_2CH$–].

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.99; H, 6.96; N, 5.65.

α-Benzamido-β,β-dimethylacrylanilide (16e). A solution of 356 mg (0.92 mmol) of *N*-benzoyl-α-anilinovaline anilide (**17c**) in 10 ml of pyridine was refluxed for 24 h. The solvent was evaporated in vacuo and the crude residue was crystallized from ethanol, giving 233 mg (86%) of **16e**: mp 288–289 °C (lit.[12] mp 288–289 °C); IR (Nujol) 3300 and 3260 (NH), 1655 and 1635 cm^{-1} (amide C=O).

Methyl (*Z*)-α-Acetamidocinnamate (16a). A mixture of 630 mg (1.45 mmol) of **1g**, 1 g (7.24 mmol) of finely divided anhydrous potassium carbonate, and 0.3 ml (4.83 mmol) of methyl iodide in 8 ml of acetone-d_6 was stirred at room temperature for 2 days. The reaction mixture was filtered through Celite, and the solvent was evaporated in vacuo. The residue was separated by chromatography on a column (4.2 × 50 cm) of silica gel (60–200 mesh) by elution with chloroform giving 345 mg (86%) of tetrachlorocatechol dimethyl ether followed by 220 mg (69%) of crude **16a**, mp 110–122 °C. Crystallization twice from benzene gave 130 mg of pure **16a**: mp 127–127.5 °C (lit.[13] mp 125–126 °C); IR (Nujol) 3200 and 3150 (NH), 1725 (C=O), 1640 cm^{-1} (C=O).

2-(Phthalimidomethyl)-4-benzylidene-2-oxazolin-5-one (19). To a solution of 1.03 g (2.91 mmol) of phthaloylglycylphenylalanine (**18**) in 5 ml of acetic anhydride containing 1 drop of pyridine was added 651 mg (2.65 mmol) of o-chloranil, and after 2 h 0.5 ml of pyridine was added. After standing for 1 day, the reaction mixture was filtered, and the solid precipitate was dried in vacuo giving 851 mg (96%) of crude **19**, mp 215–220 °C. Crystallization from ethyl acetate–hexane gave 445 mg (50%) of an analytical sample of **19**: mp 232–233 °C; UV (95% ethanol) λ_{max} 333 nm (ϵ 22 500); IR (Nujol) 1810 and 1780 (C=O), 1665 cm^{-1} (C=N); NMR (Me_2SO-d_6), 90 MHz) δ 8.23–8.02 (m, 2 H, ortho H's of C_6H_5CH=), 7.94 (s, 4 H, phthaloyl H's), 7.48–7.36 (m, 3 H, meta and para H's of C_6H_5CH=), 7.33 (s, 1 H, C_6H_5CH=), and 4.90 ppm (s, 2 H, CH_2); ^{13}C (Me_2SO-d_6) 166.8, 166.3, and 163.3 (amide C=O, oxazolin C=O, C=N), 134.8, 132.7, 132.0, 131.4, 128.8, and 123.4 (aromatic and vinyl), 35.5 ppm (CH_2N); mass spectrum *m/e* (rel intensity) 332 (41), 188 (22), 161 (42), 160 (45), 133 (19), 116 (18), 104 (42), 89 (28), 77 (50), 76 (50), 63 (21), 51 (39), 50 (39), 39 (13).

Anal. Calcd for $C_{19}H_{12}N_2O_4$: C, 68.67; H, 3.64; N, 8.43. Found: C, 68.75; H, 3.64; N, 8.43.

***N*-Phthaloylglycinedehydrophenylalanine Ethyl Ester (20).** To a solution of 1 ml of 0.5 N sodium ethoxide in 25 ml of absolute ethanol, 200 mg (0.69 mmol) of **19** was added. After stirring for 30 min at room temperature the reaction mixture was poured into a flask containing 4 ml (7.0 mequiv) of Amberlite IR-120H resin in 4 ml of ethanol. After 30 min, the resin was removed by filtration and the solvent was evaporated in vacuo. The crude residue was crystallized from 2:1 ethanol–watr, giving 200 mg (88%) of **20**: mp 200–202 °C (lit.[6] 200–201 °C); IR (KBr) 3270, 1775, and 1730 (C=O), 1690 and 1650 cm^{-1} (amide C=O).

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Registry No.—**1a**, 60422-60-8; **1b**, 60422-61-9; **1c**, 60422-62-0; **1d**, 60422-63-1; **1e**, 60422-64-2; **1f**, 60422-65-3; **1g**, 60676-46-2; **2a**, 60422-66-4; **2b**, 60422-67-5; **2d**, 56538-58-0; **2e**, 60442-68-6; **3a**, 60422-70-0; **3b**, 60676-45-1; **4**, 60422-77-7; **5a**, 60676-48-4; **5b**, 60422-81-3; **5c**, 60422-82-4; **5d**, 60676-49-5; **6**, 60676-50-8; **7a**, 60422-83-5; **7c**, 60422-84-6; **9**, 7554-10-1; **12**, 60422-80-2; **16a**, 60676-51-9; **16b**, 26924-22-1; **16c**, 60676-52-0; **16d**, 27573-05-3; **16e**, 60676-53-1; **18**, 60676-54-2; **19**, 60676-55-3; **20**, 55424-41-4; $HO_2CCH(R)NHCOR'$ (R = $PhCH_2$; R' = Ph), 2901-76-0; $HO_2CCH(R)NHCOR'$ (R = $(CH_3)_2CH$; R' = Ph), 2901-80-6; $HO_2CCH(R)NHCOR'$ (R = CH_3; R' = Ph), 1205-02-3; $HO_2CCH(R)NHCOR'$ (R = H; R' = Ph), 495-69-2; $HO_2CCH(R)NHCOR'$ (R = Ph; R' = Ph), 29670-63-1; $HO_2CCH(R)NHCOR'$ (R = $(CH_3)_2CHCH_2$; R = CH_3), 17966-67-5; o-chloranil, 2435-53-2; DL-phenylalanine, 150-30-1; aniline, 62-53-3; benzyl mercaptan, 100-53-8.

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Structure of Satratoxin H, a Metabolite of *Stachybotrys atra*. Application of Proton and Carbon-13 Nuclear Magnetic Resonance

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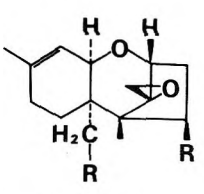
The structure of satratoxin H, a toxic metabolite of Stachybotrys atra, has been shown to be **4a** by spectroscopic studies. Satratoxin H is a macrocyclic dilactone derivative of the sesquiterpene 12,13-epoxytrichothec-9-ene and is structurally similar to roridin E, a known metabolite of *Myrothecium verrucaria*. It is most probably one of the causative agents of stachybotryotoxicosis, a food-borne disease which has affected both livestock and humans and which presents a potentially serious public health hazard.

Stachybotryotoxicosis is a food-borne disease which has affected both livestock and humans and which presents a potentially serious public health hazard.[1] The disease results from eating foods contaminated with toxic metabolites of the fungus *Stachybotrys atra*. Recent work in our laboratories has demonstrated that several derivatives of 12,13-epoxytrichothec-9-ene (**1a**) are produced by this mold and are most probably the cause of this disease.[2] Two of these metabolites, initially designated satratoxins C[3] and D,[2] were found by thin layer chromatography and ^1H NMR and mass spectral examination to be, in fact, the trichothecenes verrucarin J (**2**)[4] and roridin E (**3**),[5] respectively, reported by Tamm and co-

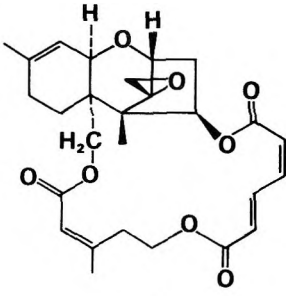
Table I. ^{1}H NMR Data[a] of Roridin E (3), Satratoxin H (4a), and Satratoxin H Diacetate (4b)

Position	3[b,c]	4a[d]	4b[c]
2	3.8 m	3.9 m	3.8 m
3	2.5 m	2.45 dd (7.5, 15)	2.5 m
3	2 m	2.20 dt (4, 5, 15)	2.2 m
4	6.22 dd (4, 8)	5.9 m	5.9 m
7	2 m	1.9 m	2 m
8	2 m	2.1 m	2 m
10	5.5 d (5)	5.46 d (5)	5.5 d (5)
11	3.7 m	3.62 d (5)	3.65 d (5)
13	3.0[e] AX (4)	2.81 d (4)	2.85 d (4)
		3.12 d (4)	3.15 d (4)
14	0.82 s	0.83 s	0.85 s
15	4.15[e] AX (12)	3.88 d (12)	3.86 d (12)
		4.56 d (12)	4.54 d (12)
16	1.75 s	1.74 s	1.75 s
2′	5.98 s	5.85 d (2)	5.85 s
4′A	2.4–2.7[f] m	3.74 dt (3, 10)	3.8 m
4′B		2.6 m	2.6 m
5′	3.5–4.0 m	3.9 m	3.8 m
7′	5.7–6.0 m	6.09 d (17.5)	6.05 d (17.5)
8′	7.53 dd (11, 15)	7.36 dd (10.5, 17.5)	7.4 dd (10.5, 17.5)
9′	6.58 t (11)	6.63 t (10.5)	6.65 t (10.5)
10′	5.75 d (11)	5.91 d (10.5)	5.9 d (10.5)
12	2.30 d (1.5)	3.97 s	5.3 s
13′	3.7 q (6)	4.38 q (7)	5.6 q (7)
14′	1.22 d (6)	1.16 d (7)	1.1 d (7)

[a] In $CDCl_3$, parts per million from Me_4Si, J values in hertz in parentheses. [b] Reference 4. [c] Spectra recorded at 100 MHz. [d] Spectra recorded at 300 MHz. [e] Center of AX system. [f] Both protons reported in this region.



1a, R=H
1b, R=OH



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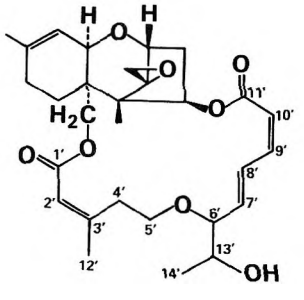

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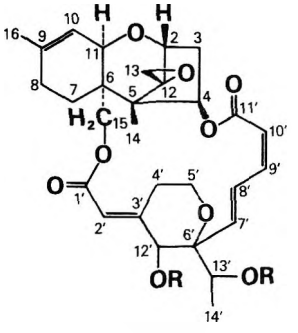


4a, R=H
4b, R=Ac

workers. We now describe spectral studies which show that the structure of another *S. atra* metabolite, designated satratoxin H, is **4a**.

Satratoxin H, $C_{29}H_{36}O_9$, is hydrolyzed in methanolic sodium hydroxide to the dialcohol verrucarol (**1b**).[2] This product accounts for 15 carbon atoms, two ethereal oxygen atoms, and five of the 12 elements of unsaturation. The presence of two alcohol groups in the product and an analogy to the congeners verrucarin J (**2**) and roridin E (**3**) imply that satratoxin H is a cyclic ester of a dicarboxylic acid and the dialcohol (**1b**), a conclusion amply supported by the ^{13}C NMR spectrum (vide infra). Thus, the functional character of a total of six oxygen atoms (two ester and two ether groups) and a total of eight elements of unsaturation are accounted for.

Signals in the 300-MHz ^{1}H NMR spectrum (Table I) arising from the verrucarol nucleus are readily identified.[6] Most notable are the resonances at 0.83 and 1.74 ppm due to the methyl groups at positions 14 and 16, respectively, and the AX pattern centered at 3 ppm, J = 4 Hz, due to the epoxide at position 13. A doublet at 4.56 ppm, J = 12 Hz, was shown by an INDOR experiment (at 100 MHz) to be coupled to a doublet in the complex at 3.8 ppm; the two protons correspond to the C-15 methylene group. An AX system of J = 5 Hz was readily assigned to the olefinic proton, H-10 (5.46 ppm), and the adjacent methine proton, H-11 (3.62 ppm). With the aid of published spectral studies, two broad peaks comprising four protons at 1.9 and 2.1 ppm could be assigned to the methylene groups of C-7 and C-8, respectively. Signals of suitable multiplicities for H-3α (2.45 ppm) and H-3β (2.20 ppm) were visible, but the multiplets of H-2 and H-4 were obscured in complex groups at 3.9 and 5.9 ppm, respectively.

Satratoxin H reacts with acetic anydride in pyridine to form a diacetate of molecular weight 612, identifying two of the remaining three oxygen atoms as hydroxyl groups. Four elements of unsaturation remain to be identified.

The ultraviolet absorption of satratoxin H suggested that

Table II. ^{13}C NMR Data[a] of Satratoxin H (4a) and Roridins A (5a), D (5b), and H (5c)

Position	4a	5a[b]	5b[b]	5c[b]
2	79.1 d	78.8 d	78.8 d	79.0 d
3	34.4 t	34.6 t	34.9 t	34.8 t
4	74.2 d	74.2 d	74.3 d	74.0 d
5	49.0 s	49.1 s	49.0 s	48.9 s
6	43.4 s	43.6 s	43.1 s	43.2 s
7	20.4 t	20.0 t	20.4 t	20.5 t
8	27.6 t	27.5 t	27.4 t	27.6 t
9	140.2 s	140.4 s	140.1 s	139.9 s
10	119.0 d[c]	118.2 d[c]	118.4 d[c]	118.6 d[c]
11	68.2 d	66.9 d	66.9 d	67.6 d
12	65.4 s	64.9 s	65.1 s	65.3 s
13	48.0 t	47.4 t	47.4 t	47.3 t
14	7.6 q	7.2 q	6.8 q	7.0 q
15	64.2 t	64.2 t	64.3 t	63.0 t
16	23.3 q	22.9 q	22.9 q	22.9 q
1′	166.2 s[d]	174.5 s	167.8 s	166.0 s
2′	119.0 d[c]	75.3 d	57.9 d	119.0 d[c]
3′	155.1 s	36.7 d	62.9 s	154.4 s
4′	25.3 dd	33.0 t	39.4 t	47.7 t
5′	60.4 t	69.5 t	67.3 t	100.8 d
6′	81.4 s	83.7 s	85.3 s	81.9 s
7′	134.2 d[e]	139.0 d	138.1 d	134.6 d
8′	132.2 d[e]	126.0 d	126.2 d	126.2 d
9′	143.0 d	143.6 d	142.9 d	142.5 d
10′	120.4 d[c]	117.2 d[c]	117.8 d[c]	118.9 d[c]
11′	167.0 s[d]	166.3 s	166.1 s	166.0 s
12′	73.7 d	14.4 q	17.2 q	18.2 q
13′	69.7 d	70.4 d	70.5 d	76.8 d
14′	15.7 q	18.0 q	17.9 q	16.3 q

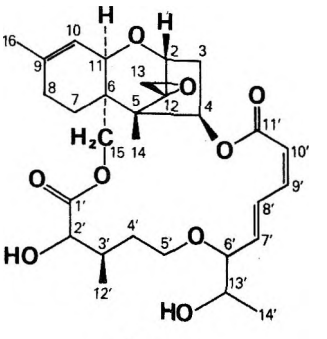
[a] In $CDCl_3$, parts per million from Me_4Si. [b] W. Breitenstein and C. Tamm, *Helv. Chim. Acta*, 58, 1172 (1975). [c,d,e] These signals could not be more specifically assigned.

this metabolite retained the unsaturated systems common to the roridin and verrucarin groups, in which one ester is conjugated with a double bond and the other with a diene system. The olefinic protons visible in the ^1H NMR spectrum supported the existence of the diene, displaying peaks with couplings suitable to a cis–trans diene attached to a fully substituted carbon atom. A single peak in the olefinic region remained to be assigned, a doublet at 5.85 ppm, $J = 2$ Hz. This chemical shift is suitable for the α proton of an acrylic ester residue; the coupling is that of an allylic proton, and shows the β carbon to be fully substituted.

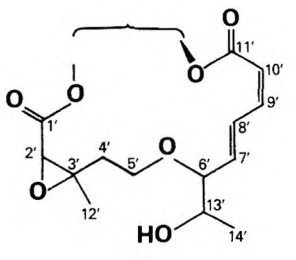
At midfield, a quartet at 4.38 ppm coupled to a methyl group at 1.16 ppm, $J = 7$ Hz, reveals a methyl carbinol system attached to a fully substituted carbon atom; a singlet at 3.97 ppm indicates a secondary alcohol flanked by fully substituted carbon atoms. These inferences are supported by comparison of the spectrum of satratoxin H with that of the diacetate (**4b**), in which both carbinol protons are shifted downfield by approximately 1 ppm.

The ^1H NMR spectra thus support the belief that the verrucarol moiety exists unaltered in satratoxin H and show the presence of an unsaturated diester lactone system closely resembling those of known metabolites in the roridin–verrucarin group.

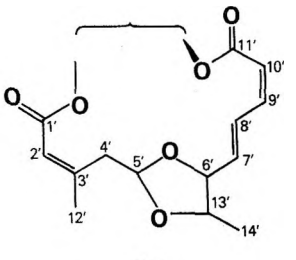
Comparison of the ^{13}C NMR chemical shift data of satratoxin H with those of roridins A, D, and H (**5a–c**) and relevant portions of related compounds[7] (Table II) supports the above conclusions and allows the identification of the 15 signals corresponding to the sesquiterpenoid verrucarol moiety. Those resonances due to the six olefinic and two carbonyl carbons of the macrocyclic dilactone are also readily distinguished. The observed chemical shifts of the carbonyl carbons provide unequivocal evidence (referred to above) for the diester system. In the single-frequency off-resonance decoupled spectra, singlets at 155.1 and 81.4 ppm confirm, moreover, the fully substituted nature of C-3′ and C-6′, while a quartet at 15.7 ppm and a doublet at 69.7 ppm are consistent with the postulated methyl carbinol pendant group.



5a



5b

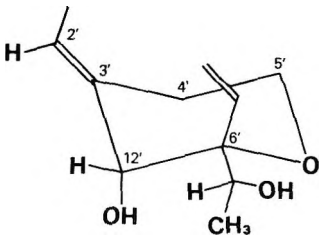


5c

Twenty-six of the 29 carbons are thus accounted for. The remaining three signals appeared in the off-resonance decoupled spectrum as follows: (1) a doublet at 73.7 ppm, (2) a triplet at 60.4 ppm, and (3) a doublet of doublets at 25.3 ppm. The first two signals correspond to methine and methylene carbons, respectively, which are attached to oxygen. The last

resonance is indicative of a methylene carbon which is not attached to oxygen and the protons of which possess widely separated chemical shifts.[8]

Knowledge of these remaining atoms may be developed as summarized in the following partial structure:



Only the methine carbon at 73.7 ppm can be the secondary alcohol group, C-12′, with the singlet proton at 3.97 ppm. It is, therefore, attached to the two fully substituted carbons identified as C-3′ and C-6′. However, as the singlet proton shows no allylic coupling, it must be in the plane of the double bond and thus be quite close to H-2′. This situation was demonstrated by a nuclear Overhauser experiment, in which irradiation of H-2′ resulted in a 24% increase in the integrated intensity of the singlet assigned to H-12′ (3.97 ppm). Additionally, decoupling irradiation at 2.6 ppm (H-4′B) caused the collapse of the H-2′ signal to a sharp singlet and altered the appearance of the complex pattern at 3.9 ppm (H-5′). The resonance at 25.3 ppm is assigned to a methylene carbon attached to C-3′, i.e. C-4′. The chemical shift of C-6′ (81.4 ppm) and that of the remaining methylene (60.4 ppm) require that they be attached to oxygen; this situation shows that the last element of unsaturation is the ether ring shown above. The fully substituted character of C-6′ shows that both the diene system and the methyl carbinol are attached here.

The structure of the macrocyclic dilactone moiety is thus complete with a single uncertainty, the stereochemistry at C-6′. There remains a question concerning its attachment to the tetracyclic verrucarol nucleus, i.e., whether C-1′ is connected to C-15 and C-11′ to C-4 or vice versa. Several lines of reasoning argue convincingly in favor of the former mode of attachment. Nine macrocyclic ring-containing trichothecenes have been reported to date: dehydroverrucarin A;[9] verrucarins A,[10] B,[10] and J;[4] roridins A,[11] D,[12] E,[5] and H;[13] and vertisporin.[14] The orientation of the various macrocyclic rings with respect to the verrucarol nucleus is the same for all of those trichothecenes. Because, in part, of similarities in chemical shifts, coupling constants, and general ^{1}H NMR spectral appearance[15] between satratoxin H and these nine trichothecenes, it is likely that the dilactone system of satratoxin H is attached to the sesquiterpenoid verrucarol nucleus in the same manner as the other macrocyclic rings (structure 4).

In addition, as previously stated, two of the metabolites which were isolated with satratoxin H proved to be compounds listed above, viz., verrucarin J and roridin E. From a biogenetic point of view, it is highly unlikely that the mold *S. atra* would produce two metabolites in which a macrocyclic ring is attached to a central nucleus in one manner and a third metabolite in which this mode of attachment is completely reversed.

The ^{13}C chemical shift data presented in Table II also offer compelling evidence for attachment of the dilactone ring of satratoxin H as depicted in structure **4**. Ellison and Kotsonis[7a] and Hanson and co-workers[7b] have demonstrated that subtle structural modifications can affect the chemical shifts of distant carbons in trichothecene systems. Apparently the chemical shifts of those carbons of the verrucarol nucleus close to the macrocyclic ring are sensitive to structural variations in the dilactone ring. The chemical shifts of such close-lying carbons (viz., carbons 4–8 and 15) in satratoxin H and roridins A, D, and H are very nearly identical (Table II), with average differences being of the order of 0.1 ppm. The dilactone system of satratoxin H is, therefore, most probably connected to the sesquiterpenoid moiety in the manner indicated.

The structure of satratoxin H represents an obvious variation on the biogenetic pathway of the roridins,[16] with the addition of a hydroxyl group on C-12′ and a dehydrogenative ring formation between C-6′ and C-12′.

Experimental Section

Satratoxin H was isolated according to the method of Eppley and Bailey.[2]

^{1}H NMR spectra of satratoxin H (no. 1603) were recorded by Dr. T. Suzuki on a Varian SC 300 spectrometer at the Institute of Polymer Science of the University of Akron, Akron, Ohio. Those of the diacetate derivative of satratoxin H were obtained on a Varian XL-100-15 spectrometer.

Proton-decoupled and single-frequency off-resonance decoupled ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.20 MHz.

Registry No.—**3,** 16891-85-3; **4a,** 53126-64-0; **4b,** 60538-74-1; **5a,** 14729-29-4; **5b,** 14682-29-2; **5c,** 29953-50-2.

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Four New Mycotoxins of *Aspergillus clavatus* Related to Tryptoquivaline

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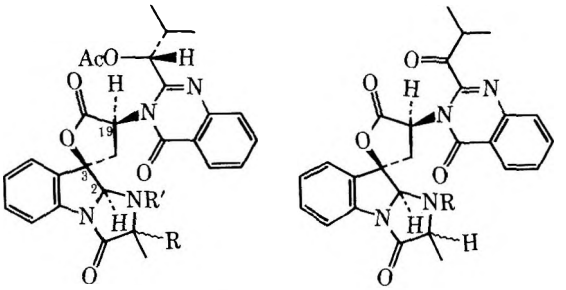
The hydroxylamine nortryptoquivaline (2) and the three secondary amines deoxytryptoquivaline (3), deoxynortryptoquivaline (4), and deoxynortryptoquivalone (8) were found to be toxic metabolites of *Aspergillus clavatus*. They were accompanied by the two previously described tremor producing agents tryptoquivaline (1) and nortryptoquivalone (7). The only weakly basic secondary amines 3, 4, and 8 were oxidized to the corresponding hydroxylamines 1, 2, and 7 with *m*-chloroperbenzoic acid.

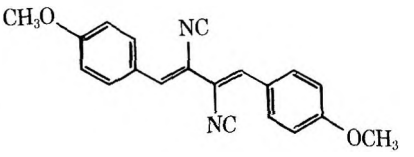
A strain of the fungus *Aspergillus clavatus* (NRRL-5890) collected from mold-damaged rice produced the two highly toxic, tremor inducing metabolites tryptoquivaline (1) and nortryptoquivalone (7).[3] The *p*-bromophenylurethane of a transformation product of tryptoquivaline was utilized in the structure determination by x-ray crystallography while spectral data left little doubt that nortryptoquivalone[4] has structure 7, but this conclusion remains to be confirmed by chemical correlation.

More recently we had occasion to examine another strain of *Aspergillus clavatus* (strain MIT-M-18) for the presence of mycotoxins. Its identity was established by the Centraalbureau voor Schimmelcultures, Baarn, The Netherlands. The fungus was one of several collected from mold-infested rice found in a Thai household where a child died of an unidentified toxicosis.[5] Solid substrate, agitated fermentation on pearled barley[6] gave optimum yields of secondary metabolites and individual components were isolated by high-pressure liquid and thin layer chromatography. The least and most polar fractions contained the known fungal metabolites xanthocillin-X dimethyl ether (9)[7] and kotanin (10),[8] respectively. From the intermediate fractions nortryptoquivalone (7) and tryptoquivaline (1) could be isolated in crystalline form. These two metabolites were now found to exhibit very similar circular dichroism spectra (see Experimental Section) tentatively suggesting identical *relative* configurations at C_2, C_3, and C_{19}.[9]



1, R = CH_3; R′ = OH
2, R = H; R′ = OH
3, R = CH_3; R′ = H
4, R = H; R′ = H
5, R = H; R′ = OAc
6, R = H; R′ = Ac

7, R = OH
8, R = H



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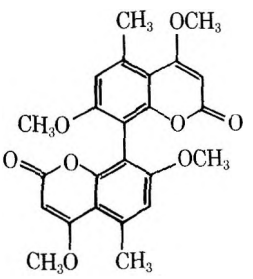

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The least polar of the new metabolites, mp 256–258 °C, further characterized by its acetate 5, had the composition $C_{28}H_{28}N_4O_7$. Its ultraviolet absorption spectrum was indistinguishable from that of tryptoquivaline (1) and all infrared absorptions associated with functional groups were identical in the two spectra. The proton magnetic resonance spectrum of the new metabolite was identical with that of tryptoquivaline (1) except that signals associated with the geminal dimethyl group in the latter were replaced by those of a secondary methyl function. The first of the new metabolites thus is nortryptoquivaline (2) and its circular dichroism spectrum indicates the relative stereochemistry shown.

A second new metabolite, mp 150–152 °C, was found to have the composition $C_{29}H_{30}N_4O_6$. It thus differs from tryptoquivaline (1) by the absence of an oxygen atom. The suggestion that it might be deoxytryptoquivaline (3) was strengthened by a negative triphenyltetrazolium chloride test for hydroxylamines[12] and confirmed by oxidation to tryptoquivaline (1) with *m*-chloroperbenzoic acid. Deoxytryptoquivaline (3) is only weakly basic and was not extracted from organic solvents by 1 N aqueous hydrochloric acid.

The third of the new mycotoxins, mp 192–193 °C, with the composition $C_{26}H_{24}N_4O_5$ was deoxynortryptoquivalone (8) oxidized to nortryptoquivalone (7) by *m*-chloroperbenzoic acid.

A negative color test for hydroxylamines suggested that the last metabolite, mp 158–160 °C, $C_{28}H_{28}N_4O_6$, is also a secondary amine and its oxidation to nortryptoquivaline (2) with peracid established it to be deoxynortryptoquivaline (4). Direct comparison[10] with a substance called FTD (later shown to be norisotryptoquivaline[11]) elaborated by *Aspergillus fumigatus* proved their nonidentity. All four of the new metabolites are toxic and full toxicological data will be reported by Professor Gerald Wogan elsewhere. None have activity against the mycotoxin assay organism, *Bacillus megaterium*.[6] On the other hand, the xanthocillin-X dimethyl ether showed antibacterial activity when assay disks were dipped into solutions containing 125 μg/ml or higher.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are corrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Ultraviolet (UV) spectra were determined on a Cary 14 recording spectrophotometer. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 567 grating spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a Hitachi Perkin-Elmer R-22 90-MHz instrument and are given in parts per million (δ) downfield from an internal tetramethylsilane standard;

the abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. High-resolution mass spectra (HRMS) were determined at 70 eV on a CEC-110B (Du Pont) instrument. Circular dichroism (CD) spectra were measured on a Cary 60 spectrophotometer. High-pressure liquid chromatography (HPLC) was performed using a Waters Associates liquid chromatograph with a 7 ft × 0.375 in. o.d. Porasil A (0.037–0.075 mm particle size) column, and about 20 mg per separation.

Production and Isolation of the Secondary Fungal Metabolites. *A. clavatus* (strain MIT-M-18) was grown on barley in Fernbach flasks on a shaker at 30 °C for 10 days.[6] The growth medium was extracted with dichloromethane and filtered, and the filtrate evaporated in vacuo. After the residue was suspended in petroleum ether the pale yellow precipitate (PEI) was collected. The PEI (9.2 g) was chromatographed on a silica gel column (250 g, EM Reagents, 0.063–0.200 mm particle size) with mixtures of hexane–chloroform, chloroform, chloroform–ethyl acetate, and ethyl acetate, to give six crude fractions (fractions I–VI, as determined by TLC, fraction I being eluted first). Fraction III (375 mg) was rechromatographed on silica gel (15 × 1000 mm, 85 g, Woelm, 0.032–0.063 mm particle size) using chloroform–hexane (7:3 v/v) as solvent to give xanthocillin-X dimethyl ether (**9**, 113 mg).

Xanthocillin-X Dimethyl Ether (9). Yellow needles from dichloromethane–hexane: mp 186 °C dec; UV max (95% C_2H_5OH) 238 nm (ε 13 600), 297 (12 200), and 364 (46 400); IR ($CHCl_3$) 2122, 1602, 1510, 1260, 1180, and 1031 cm^{-1}; NMR ($CDCl_3$) δ 7.71 (d, 2, J = 9 Hz), 7.01 (s, 1), 6.93 (d, 2, J = 9 Hz), and 3.87 (s, 3); HRMS *m/e* (rel intensity) found 316.11936 (100) (calcd for $C_{20}H_{16}N_2O_2$, 316.12117).

Fraction IV was rechromatographed on silica gel (25 × 1000 mm, 260 g, Woelm, 0.032–0.063 mm particle size) using 10% acetone in benzene as solvent to give five fractions (IVA–IVE). Fraction IVA was rechromatographed by HPLC using 3% 2-propanol in hexane as solvent to give nortryptoquivalone (**7**, faster moving component, 40 mg), and tryptoquivaline (**1**, 200 mg).

Nortryptoquivalone (7). Colorless prisms from dichloromethane–hexane: mp 208–209 °C; $[\alpha]^{25}D$ 255° (*c* 0.30, $CHCl_3$); UV max (95% C_2H_5OH) 228 nm (sh, ε 31 300), 232 (31 800), 253 (sh, 16 900), 278 (7600), 289 (sh, 6500), 304 (5400), and 316 (sh, 4500); IR ($CHCl_3$) 3500, 2960, 2935, 2875, 1783, 1725, 1705, 1672, 1609, 1484, 1469, and 1406 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 3, J = 7 Hz), 1.32 (d, 3, J = 7 Hz), 1.60 (d, 3, J = 7 Hz), 3.10 (d of d, 1, J = 10 and 13 Hz), 3.48 (d of d, 1, J = 10 and 13 Hz), 4.13 (m, 1, J = 7 Hz), 4.36 (q, 1, J = 7 Hz), 5.24 (s, 1), 5.51 (t, 1, J = 10 Hz), 7.12–7.95 (m, 7), and 8.52 (m, 1); HRMS *m/e* (rel intensity) found 488.17037 (100) [calcd for $C_{26}H_{24}N_4O_6$, 488.16958 (M^+)]; CD (95% C_2H_5OH) 256 nm (θ −12 500), 273 (0), 298 (12 000), and 342 (0), estimated absolute error in θ ±2500 deg cm^2/dmol; positive TTC and 2,4-DNP tests.

Tryptoquivaline (1). Colorless prisms from dichloromethane–hexane mixture: mp 155–157 °C; $[\alpha]^{25}D$ 130° (*c* 0.22, $CHCl_3$); UV max (95% C_2H_5OH) 228 nm (ε 41 200), 232 (sh, 40 200), 252 (sh, 19 500), 268 (sh, 10 900), 279 (9500), 307 (3700), and 319 (3000); IR ($CHCl_3$) 3490, 2980, 2940, 2880, 1786, 1728, 1672, 1610, 1485, 1470, and 1410 cm^{-1}; NMR ($CDCl_3$) δ 1.01 (d, 3, J = 7 Hz), 1.13 (d, 3, J = 7 Hz), 1.47 (s, 3), 1.49 (s, 3), 2.14 (s, 3), 2.57 (m, 1), 2.96 (d of d, 1, J = 10 and 13 Hz), 3.16 (d of d, 1, J = 10 and 13 Hz), 4.92 (s, 1), 5.52 (d, 1, J = 9 Hz), 5.63 (t, 1, J = 10 Hz), 7.00–7.78 (m, 7), and 8.67 (m, 1); HRMS *m/e* (rel intensity) found 546.21554 (100) [calcd for $C_{29}H_{30}N_4O_7$, 546.2114 (M^+)]; CD (95% C_2H_5OH) 258 nm (θ −17 500), 282 (0), 305 (7500), and 327 (0), estimated absolute error in θ ±2500 deg cm^2/dmol; positive TTC test.

Fraction IVB was purified by HPLC using 5% 2-propanol in hexane as solvent to give nortryptoquivaline (**2**, 272 mg).

Nortryptoquivaline (2). Colorless prisms from dichloromethane–hexane mixture: mp 256–258 °C; $[\alpha]^{25}D$ 170° (*c* 0.64, $CHCl_3$); UV max (95% C_2H_5OH) 228 nm (ε 43 600), 233 (sh, 42 000), 254 (sh, 18 700), 267 (sh, 11 900), 279 (10 200), 306 (4500), and 319 (3500); IR ($CHCl_3$) 3490, 2980, 2940, 2880, 1790, 1728, 1670, 1610, 1485, 1471, and 1410 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (d, 3, J = 7 Hz), 1.16 (d, 3, J = 7 Hz), 1.58 (d, 3, J = 7 Hz), 2.16 (s, 3), 2.57 (m, 1), 2.94 (d of d, 1, J = 10 and 13 Hz), 3.18 (d of d, 1, J = 10 and 13 Hz), 4.28 (q, 1, J = 7 Hz), 5.10 (s, 1), 5.54 (d, 1, J = 9 Hz), 5.65 (t, 1, J = 10 Hz), 7.01–7.79 (m, 7), and 8.12 (m, 1); HRMS *m/e* (rel intensity) found 532.19525 (100) [calcd for $C_{28}H_{28}N_4O_7$, 532.19580 (M^+)]; CD (95% C_2H_5OH) 254 nm (θ −19 000), 287 (0), 307 (7000), and 325 (0), estimated absolute error in θ ±2500 deg cm^2/dmol; positive TTC test.

Fraction IVC was separated by HPLC using 10% 2-propanol in hexane as solvent to give deoxytryptoquivaline (**3**, faster moving component, 45 mg) and deoxynortryptoquivalone (**8**, 63 mg).

Deoxytryptoquivaline (3). White needles from dichloromethane–hexane mixture: mp 150–152 °C; $[\alpha]^{25}D$ 56.8° (*c* 0.78, $CHCl_3$); UV max (95% C_2H_5OH) 227 nm (ε 44 500), 232 (sh, 41 900), 252 (sh, 18 500), 267 (sh, 12 000), 278 (sh, 10 300), 304 (3300), and 318 (sh, 2700); IR ($CHCl_3$) 3360, 3310, 2980, 2935, 2875, 1790, 1720, 1676, 1604, 1483, and 1469 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (d, 3, J = 7 Hz), 1.20 (d, 3, J = 7 Hz), 1.53 (s, 6), 2.16 (s, 3), 2.54 (m, 1), 3.06 (d, 2, J = 10 Hz), 5.24 (s, 1), 5.52 (d, 1, J = 9 Hz), 5.65 (t, 1, J = 10 Hz), 7.11–7.74 (m, 7), and 8.20 (m, 1); HRMS *m/e* (rel intensity) found 530.21527 (100) [calcd for $C_{29}H_{30}N_4O_6$, 530.21653 (M^+)]; negative TTC test.

Deoxynortryptoquivalone (8). Fine white needles from diethyl ether: mp 192–193 °C; $[\alpha]^{25}D$ 171° (*c* 0.79, $CHCl_3$); UV max (95% C_2H_5OH) 232 nm (ε 32 400), 288 (9250), and 320 (sh, 6250); IR ($CHCl_3$) 3360, 2980, 2935, 2880, 1790, 1705, 1680, 1610, 1588, 1484, and 1469 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (d, 3, J = 7 Hz), 1.30 (d, 3, J = 7 Hz), 1.56 (d, 3, J = 7 Hz), 3.02 (d of d, 1, J = 10 and 13 Hz), 3.32 (d of d, 1, J = 10 and 13 Hz), 4.08 (m, 1, J = 7 Hz), 4.12 (q, 1, J = 7 Hz), 5.36 (s, 1), 5.48 (t, 1, J = 10 Hz), 7.04–7.84 (m, 7), and 8.24 (m, 1); HRMS *m/e* (rel intensity) found 472.17276 (100) [calcd for $C_{26}H_{24}N_4O_5$, 472.17467 (M^+)]; negative TTC test, but positive 2,4-DNP test.

Fraction IVD was purified by chromatography on a silica gel column (85 g, 15 × 1000 mm, Woelm, 0.032–0.063 mm particle size) using 20% ethyl acetate in dichloromethane as solvent to give pure deoxynortryptoquivaline (**4**, 361 mg).

Deoxynortryptoquivaline (4). Colorless prisms from diethyl ether: mp 158–160 °C; $[\alpha]^{25}D$ 69.5° (*c* 0.82, $CHCl_3$); UV max (95% C_2H_5OH) 228 nm (ε 43 900), 233 (sh, 40 100), 254 (sh, 15 600), 268 (11 700), 278 (sh, 10 500), 305 (4100), and 317 (3300); IR ($CHCl_3$) 3360, 2975, 2935, 2880, 1790, 1724, 1676, 1607, and 1483 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, 3, J = 7 Hz), 1.15 (d, 3, J = 7 Hz), 1.55 (d, 3, J = 7 Hz), 2.16 (s, 3), 2.58 (m, 1), 2.87 (d of d, 1, J = 10 and 13 Hz), 3.07 (d of d, 1, J = 10 and 13 Hz), 4.12 (q, 1, J = 7 Hz), 5.22 (s, 1), 5.55 (d, 1, J = 9 Hz), 5.65 (t, 1, J = 10 Hz), 7.02–7.74 (m, 7), and 8.14 (m, 1); HRMS *m/e* (rel intensity) found 516.20420 (100) [calcd for $C_{28}H_{28}N_4O_6$, 516.20088 (M^+)]; negative TTC test.

Fraction IVE, which contained several compounds by TLC, was concentrated to about one-third of its original volume. The crystals which appeared were collected and recrystallized from chloroform–hexane to give kotanin (**10**, 900 mg).

Kotanin (10). Cubes: mp >330 °C; $[\alpha]^{23}D$ 40.0 (c 1.65, $CHCl_3$); UV max (95% C_2H_5OH) 236 nm (sh, ε 26 900), 253 (sh, 13 600), 296 (sh, 29 000), 308 (33 900), and 318 (sh, 27 600); IR ($CHCl_3$) 3000, 2940, 2850, 1702, 1612, 1590, 1455, and 960 cm^{-1}; NMR ($CDCl_3$) δ 6.73 (s, 1), 5.50 (s, 1), 3.93 (s, 3), 3.80 (s, 3), and 2.73 (s, 3); HRMS *m/e* found 438.13000 (calcd for $C_{24}H_{22}O_8$, 438.13147).

Acetylation of Nortryptoquivaline (2). To a stirred solution of nortryptoquivaline (33 mg, 0.062 mmol) in pyridine (1.5 ml) at 0 °C under an argon atmosphere was added acetic anhydride (1.5 ml). After 5 h at 0 °C, the reaction mixture was poured into cold dilute HCl and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl, dried (anhydrous Na_2SO_4), evaporated in vacuo, and chromatographed (HPCL, 10% ethyl acetate in dichloromethane) to give nortryptoquivaline acetate (**5**, 31.7 mg, 89% yield), colorless prisms from diethyl ether: mp 155–157 °C; $[\alpha]^{25}D$ 159° (*c*, 0.16, $CHCl_3$); UV max (95% C_2H_5OH) 228 nm (ε 41 500), 233 (sh, 39 200), 253 (sh, 19 300), 268 (sh, 12 300), 279 (10 900), 305 (4100), and 319 (3200); IR ($CHCl_3$) 2980, 2940, 2880, 1796, 1730, 1689, 1600, 1485, and 1470 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (d, 3, J = 7 Hz), 1.21 (d, 3, J = 7 Hz), 1.52 (d, 3, J = 7 Hz), 2.16 (s, 3), 2.40 (s, 3), 2.62 (m, 1), 2.98 (d of d, 1, J = 10 and 13 Hz), 3.30 (d of d, 1, J = 10 and 13 Hz), 4.55 (q, 1, J = 7 Hz), 5.39 (s, 1), 5.49 (d, 1, J = 9 Hz), 5.72 (t, 1, J = 10 Hz), 7.20–7.78 (m, 7), and 8.11 (m, 1); HRMS *m/e* no molecular ion, found 514.18434 [calcd for $C_{28}H_{26}N_4O_6$, 514.18523 ($M^+ - CH_3COOH$),[13] 470.19604, calcd for $C_{27}H_{26}N_4O_4$, 470.19540 ($M^+ - CH_3COOH$, $-CO_2$)].

Acetylation of Deoxynortryptoquivaline (4). A stirred solution of deoxynortryptoquivaline (**4**, 35.8 mg, 0.07 mmol) in pyridine (1.5 ml) and acetic anhydride (1.5 ml) under argon was heated to 60–65 °C for 6 h. The reaction mixture was diluted with ethyl acetate and washed with dilute HCl, aqueous $NaHCO_3$, and saturated aqueous NaCl solutions in succession. After drying (anhydrous Na_2SO_4), the organic layer was evaporated in vacuo and chromatographed (HPLC, 15% 2-propanol in hexane) to give crystalline deoxynortryptoquivaline acetamide (**6**, 12.8 mg, 33% yield), recrystallized from dichloromethane–hexane mixture to give colorless prisms: mp 303–304 °C; $[\alpha]^{25}D$ 149° (*c* 0.27, $CHCl_3$); UV max (CH_3CN) 227 nm (ε 36 000), 230 (sh, 28 600), 270 (10 000), 280 (sh, 9400), 305 (3650), and 320 (sh, 2800); IR ($CHCl_3$) 2965, 2930, 2875, 1789, 1735, 1688, 1670, 1600, 1475, and 1468 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, 3, J = 7 Hz), 1.22 (d, 3, J = 7 Hz), 1.85 (d, 3, J = 7 Hz), 2.21 (s, 3), 2.46 (s, 3), 3.00 (d of d, 1, J = 10 and 13 Hz), 3.96 (d of d, 1, J = 10 and 13 Hz), 4.78 (q, 1, J = 7 Hz), 5.61 (t,

1, J = 10 Hz), 5.68 (d, 1, J = 9 Hz), 6.41 (s, 1), 7.24–7.84 (m, 7), and 8.24 (m, 1); HRMS m/e (rel intensity) found 558.21118 (100) [calcd for $C_{30}H_{30}N_4O_7$, 558.21145 (M^+)].

Oxidation of Deoxytryptoquivaline (3). To a stirred solution of deoxytryptoquivaline (**3**, 16.7 mg, 0.032 mmol) in dichloromethane (5 ml) at room temperature was added *m*-chloroperbenzoic acid (*m*-CPBA, 6.3 mg, 0.037 mmol). The reaction mixture was diluted with dichloromethane (20 ml) after 15 min, and washed with dilute aqueous $NaHCO_3$. The organic layer was dried (anhydrous Na_2SO_4), evaporated in vacuo, and chromatographed (HPLC, 3% 2-propanol in hexane as solvent) to give tryptoquivaline (**1**, 12.6 mg, 73% yield), identical with authentic material.

Oxidation of Deoxytryptoquivalone (8). Deoxynortryptoquivalone (**8**, 19.6 mg, 0.042 mmol) was oxidized with *m*-CPBA (8.2 mg, 0.048 mmol) to give, after workup and chromatography (HPLC, 3% 2-propanol in hexane), nortryptoquivalone (**7**, 12.6 mg, 62% yield), identical with authentic material.

Oxidation of Deoxynortryptoquivaline (4). Deoxynortryptoquivaline (**4**, 38.4 mg, 0.074 mmol) was oxidized with *m*-CPBA (14.2 mg, 0.082 mmol) to give, after workup and chromatography (HPLC, 5% 2-propanol in hexane), nortryptoquivaline (**2**, 34.3 mg, 86.6% yield) identical with authentic material.

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Registry No.—**1**, 55387-45-6; **2**, 60676-56-4; **3**, 60676-57-5; **4**, 60676-58-6; **5**, 60676-59-7; **6**, 60676-60-0; **7**, 55387-46-7; **8**, 60676-61-1; **9**, 4464-33-9; **10**, 27909-08-6.

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Podophyllotoxin Derivatives. 3.[1] The Remaining Diastereomeric C-4 Alcohols and Ketone of the L Series[2]

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The preparation of L-isopodophyllotoxin (**5**), L-isopicropodophyllin (**7**), and L-isopodophyllotoxone (**12**) is described. With these compounds the eight possible diastereomeric C-4 alcohols (toxins) and four possible C-4 ketones of the L series[2] are all known. Alcohol **5** instead of its epimer **6** was obtained by sodium borohydride reduction of **12** contrary to predictions based on previously reported reduction of DL-**12**.

In the L series, of the eight possible diastereomers of the podophyllotoxin structure (chiral centers at C-2, -3, and -4) and four of the podophyllotoxone structure (chiral centers at C-2 and -3), recent publications[1,3] left two of the alcohols and one ketone undescribed. This is a report of the preparation of these compounds, namely L-isopodophyllotoxin (**5**, 2β,3α,4β), L-isopicropodophyllin (**7**, 2α,3α,4β), and L-isopodophyllotoxone (**12**, 2β,3α) (Chart I).

The Alcohols (Toxins). Compound **5** (2β,3α,4β), previously known only as an unresolved component of a DL mixture,[4] was obtained by inversion at C-4 on treatment of **6** (2β,3α,4α) with dilute acid. Alcohol **6** had been prepared starting with **8** (2α,3α,4α) by an indirect method involving simultaneous epimerization at C-2 and cleavage of the lactone group, and subsequent relactionization of the resulting hydroxy acid (Scheme I).

Additionally **5** was derived from L-isopodophyllotoxone (**12**, see below), by $NaBH_4$ reduction. Finding **5** as the predominant (72%) and sole alcoholic reduction product was unexpected, because it had previously been reported[4] that the DL form of **12** when reduced with $Zn(BH_4)_2$ afforded DL-**6**, the C-4 epimer of DL-**5**.[5] The identity of our reduction product was established by direct spectral (ir, NMR, mass) comparisons of both the alcohol and its acetate with authentic DL samples (prepared by a different route) provided by two laboratories.[6]

Moreover **5** can be reconverted to **6**. The interconversions between **5** and **6** are analogous to the known and fully discussed[7,8] interconversions between alcohols **1** (2α,3β,4α) and **2** (2α,3β,4β). The four compounds constitute the two pairs of half-chair structures made rigid by the 2,3-trans-lactone fusion,[1] with **5** and **6** in the 2β,3α and **1** and **2** in the 2α,3β configurations. Thus the 4-OH groups in both **2** (4β) and **6** (4α), having pseudoaxial conformations, are inverted on treatment with dilute HCl, whereas the corresponding hydroxy groups in **1** (4α) and **5** (4β), being pseudoequatorial, require a two-step process (via the 4-chloro derivative) to complete the inversion.

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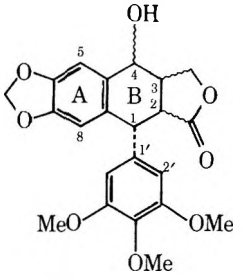
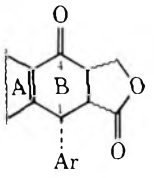
Chart I



1	podophyllotoxin	(2α,3β,4α)
2	epipodophyllotoxin	(2α,3β,4β)
3	picropodophyllin	(2β,3β,4α)
4	epipicropodophyllin	(2β,3β,4β)
5	isopodophyllotoxin	(2β,3α,4β)
6	epiisopodophyllotoxin	(2β,3α,4α)
7	isopicropodophyllin	(2α,3α,4β)
8	epiisopicropodophyllin	(2α,3α,4α)



9	isopicropodophyllone	(2α,3α)
10	podophyllotoxone	(2α,3β)
11	picropodophyllone	(2β,3β)
12	isopodophyllotoxone	(2β,3α)

In this and subsequent charts partial formulas are used, and "Ar" at C-1 indicates the α-substituted 3,4,5-trimethoxyphenyl group.

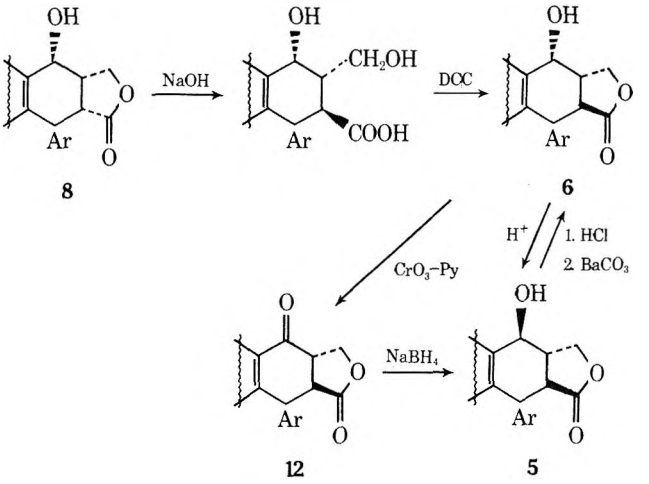
Previous tentative explanations for the supposed formation of **6** from ketone **12** have been admittedly speculative.[1,4] Now confirmation that **12** yields instead the equatorial alcohol **5** as the major reduction product provides a more consistent stereochemical picture of metal hydride reduction of the two rigid trans ketones **10** and **12**. Molecular models show that with both trans ketones, hydride attack from the less hindered side of the molecule (β side in **10**, α side in **12**) would result in the presumably more stable equatorial alcohol in each case, as is actually found experimentally.

Compound **7** (2α,3α,4β) was obtained in low yield (14%) by inversion of alcohol **8** (2α,3α,4α) in dilute acid. As with the 2β,3β-cis alcohols **3** and **4**, acid-catalyzed dehydration takes place readily,[10] but in this instance β-apopicropodophyllin (**16**) is the major product.[11] In stronger acid the proportion of elimination product increases. The structure of **7** was substantiated[12] by spectral and mass analyses, and conversion to **5**.

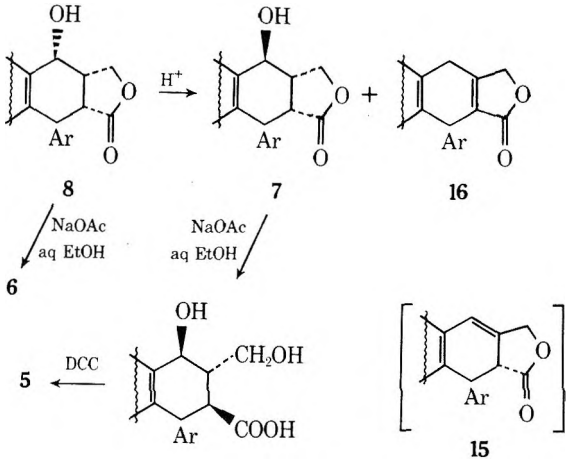
This conversion is a two-step process: inversion at C-2 with concomitant cleavage of the lactone ring by treatment with sodium acetate in aqueous alcohol, and subsequent relactonization of the resulting hydroxy acid (Scheme II). Cleavage of the lactone ring of **7** on being refluxed in NaOAc was expected, in analogy with a similar reaction of deoxyisopicropodophyllin reported by Schrecker and Hartwell.[13] However, unexpectedly, compound **8**, which has the same cis (2α,3α) configuration of **7**, under identical reaction conditions does not undergo cleavage of the lactone, but in a slow reaction is epimerized at C-2 to **6** (2β,3α,4α). The 2β,3α-deoxyisopodophyllotoxin also was cleaved to hydroxy acid according to Schrecker and Hartwell.[13]

In our earlier work[1] we found that **8** even at room temperature is cleaved by NaOH in aqueous ethanol to give the epimerized (at C-2) dihydroxy acid, and had deduced that the epimerization step precedes cleavage of the lactone. The present finding of the inverted product with lactone group

Scheme I



Scheme II



intact under milder alkaline conditions supports that sequence of reaction steps. The difference in stability of the lactone ring between the epimers **7** and **8** thus is related to the configuration of the hydroxy group at C-4. How a hydroxy group γ to the carbonyl affects the cleavage is intriguing.[14]

L-Isopodophyllotoxone (12). On the basis of the reported preparation[4] of the DL form of **12** from DL-**5** by oxidation with MnO_2, we had expected that the oxidation of optically active alcohol **6** to **12** would be straightforward. However, when the oxidation of **6** was attempted with freshly prepared MnO_2[15] following the procedure used for the DL compound,[4] the reaction proceeded sluggishly[16] and only a trace of ketonic material resulted. Changing reaction conditions to improve the yield was unproductive, and other oxidizing agents were explored. We found that the Sarett reagent (chromic anhydride–pyridine) was effective; ketone **12** was produced in 89% yield in a smooth reaction. Subsequently the diastereomeric ketones **10** and **11** were obtained from the corresponding alcohols with this reagent in yields as good as or superior to that reported with MnO_2.[4] The DL ketone (DL-**12**), prepared by the CrO_3–pyridine method from DL-**6** in 72% yield, was found to be much less soluble in organic solvents ($CHCl_3$, methanol, and acetone)[17] than the L compound.

Experimental Section[18]

L-Isopodophyllotoxin (5). 1. By Epimerization of 6. A solution of **6** (50 mg) in dioxane (10 ml) was refluxed with 2 N HCl (10 ml) for 3 h, diluted with water, and extracted with $CHCl_3$ (3 × 10 ml). Removal of solvent after washing with water and subsequent drying yielded a residue (44 mg) which was purified by preparative TLC (EtOAc–hexane, 65:35, twice). Two major components were isolated. One (R_f 0.40) was crystallized ($CHCl_3$–EtOH) and identified as

starting compound **6** (17 mg, 34%). The other product (R_f 0.46) crystallized from $CHCl_3$–EtOH as colorless needles (21 mg, 42%), mp 244–246 °C, and was characterized as L-isopodophyllotoxin: $[\alpha]_D$ −187° (c 0.70, pyridine); UV max (EtOH) 287 nm (ε 4.13) and 248 (3.72); IR (KBr) 2.95 (OH) and 5.62 μ (lactone C=O); NMR (Me_2SO) τ 6.36 (s, 3 H, –OMe), 6.30 (s, 6 H, –OMe), 4.13 (s, 2 H, $-OCH_2O-$), 3.88 (s, H, C-5) [four groups of signals remain:[19] 6.84 (perturbed t), 6.01–5.67 (perturbed multiplet), 5.48 (perturbed t), and 5.14 (d, J = 5.0 Hz)]; mass spectrum *m/e* 414 (rel intensity) (M^+, 100), 399 (30), 254 (26), 181 (24), 168 (72), and 153 (36).

Anal. Calcd for $C_{22}H_{22}O_8 \cdot \frac{1}{2}H_2O$: C, 62.41; H, 5.43. Found: C, 62.69; H, 5.43.

The product **5** was indistinguishable from DL-**5**[6] in direct comparisons by TLC, HPLC, and in their NMR, IR, and mass spectra.

2. By Reduction of Ketone 12. A. A solution of 12 (100 mg) in dioxane (20 ml) at 0 °C was treated with 80 mg of $NaBH_4$, allowed to stand for 1 h, diluted with water, and neutralized with a few drops of HOAc. The mixture was further diluted with water and extracted with $CHCl_3$ (3 × 20 ml). The $CHCl_3$ extract was processed to yield a residue which on crystallization gave colorless needles (72 mg, 72%), which were found to be identical with **5** obtained in part 1 above (mixture melting point, TLC, HPLC, IR, NMR).

B. A similar experiment carried out on 10 mg of **12** in which $Zn(BH_4)_2$[20] was used as the reducing agent, after 50 h, was processed. The residue examined by TLC and HPLC contained **5** as a minor product, and unchanged 12 as the major product. No indication of alcohol **6**[21] was seen.

Acetate of 5 was prepared with acetic anhydride in pyridine at 25 °C and crystallized from $CHCl_3$–EtOH as colorless plates: mp 232–234 °C; $[\alpha]_D$ +83.8° (c 0.8, $CHCl_3$); IR ($CHCl_3$) 5.62 (lactone C=O) and 5.77 μ (ester C=O); NMR[5] (pyridine) τ 7.83 (s, 3 H, –OCOMe), 6.32 (s, 6 H, –OMe), 6.15 (s, 3 H, –OMe), 4.08 (d, 2 H, J = 3.5 Hz, $-OCH_2O-$), 3.61 (d, H, J = 8.9 Hz, C-4), 3.40 (s, H, C-8), 3.16 (s, 2 H, C-15, -19), and 3.01 (s, H, C-5); mass spectrum m/e (rel intensity) 456 (M^+, 52) 396 (20), 168 (100) and 153 (72).

The acetates of **5** and DL-**5**[6] had identical IR, NMR, and mass spectra, and TLC properties.

Reconversion of 5 to 6.[7,8] Through a solution of **5** (50 mg) in Me_2SO (15 ml) HCl gas was passed for 2 h. The reaction product was diluted with water, extracted with $CHCl_3$ (3 × 15 ml), washed, dried, and evaporated (40 mg). TLC showed the complete disappearance of the starting compound. The residue was taken in acetone and refluxed with $BaCO_3$ (40 mg) for 4 h. The reaction product was filtered and the filtrate evaporated to dryness (32 mg). The residue, purified by preparative TLC (EtOAc–hexane, 65:35, twice), yielded two compounds[21] identified as **6** (13 mg, 36%) and unchanged **5** (8 mg, 16%) by TLC, IR, and NMR.

L-Isopicropodophyllin (7). Alcohol 8 (200 mg) in dioxane (20 ml) was refluxed in 20 ml of 0.002 N HCl for 12 h. When diluted with water, a solid (80 mg) precipitated. The filtrate was extracted with $CHCl_3$ (3 × 20 ml), washed with water, dried, and evaporated to yield 110 mg of residue. Purification by preparative TLC (EtOAc–hexane, 1:1) afforded three products. The first (R_f 0.30, 12 mg) crystallized from $CHCl_3$–MeOH, mp 261–263 °C, was identified as starting compound 8.

The second product (R_f 0.50, 28 mg, 21%[22]), which crystallized from $CHCl_3$–hexane, was characterized as L-isopicropodophyllin (**7**): mp 92–94 °C; $[\alpha]_D$ −133° ($CHCl_3$); IR (KBr) 2.90 (OH) and 5.70 μ (lactone C=O); UV max (EtOH) 287 nm (ε 3.79) and 248 (4.07); NMR (Me_2SO) τ 6.40 (s, 3 H, –OMe), 6.36 (s, 6 H, –OMe), 5.36 (d, H, J = 3.0 Hz, C-4), 4.06 (s, 2 H, $-OCH_2O-$), 3.63 (s, 2 H, C-15, -19), 3.17 (s, H, C-8), and 2.97 (s, H, C-5), several groups of multiplets between 7.30 and 5.25 remain unassigned;[19] mass spectrum *m/e* (rel intensity) 414 (M^+, 30), 396 (51), 246 (30), 202 (42), 181 (40), 168 (100), and 153 (58).

Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.67; H, 5.35.

The product 7 was found to be identical with a sample provided by Dr. von Wartburg[12] according to comparisons by IR and NMR.

The third product (R_f 0.60, 40 mg) crystallized from MeOH: mp 220–222 °C; $[\alpha]_D$ +92° (c 0.85, $CHCl_3$); IR ($CHCl_3$) 5.65 μ (lactone C=O); UV max (EtOH) 290 nm (ε 3.51) and 254 (1.79); mass spectrum *m/e* (rel intensity) 396 (M^+, 4), 168 (100), and 153 (60). It was identified as β-apopicropodophyllin (**16**) by direct comparison (mixture melting point, TLC, and IR) with an authentic sample prepared from picropodophyllin (**3**).[23]

Acetate of 7, prepared as for the acetate of **5,** was crystallized from hexane: mp 86–88 °C; $[\alpha]_D$ −105.0° (c 0.84, $CHCl_3$); IR ($CHCl_3$) 5.68 (lactone C=O) and 5.75 μ (ester C=O); NMR (pyridine) τ 7.88 (s, 3 H, –OCOMe), 6.27 (s, 6 H, –OMe), 6.14 (s, 3 H, –OMe), 4.04 (d, 2 H, $-OCH_2O-$), 3.81 (d, H, J = 4.4 Hz, C-4), 3.10 (s, 2 H, C-15, -19); mass spectrum *m/e* (rel intensity) 456 (M^+, 10), 396 (75), 379 (24), 168 (100), and 153 (56).

Conversion of 7 to 5 (via Inversion at C-2, Cleavage, and Relactonization). A solution of **7** (30 mg) in 50% aqueous EtOH (25 ml), after being refluxed with NaOAc (50 mg) for 1 h, was diluted with water, extracted with $CHCl_3$ (3 × 10 ml), dried, and evaporated. To the residue (22 mg) dissolved in $CHCl_3$ was added DCC (20 mg). After 1 h the solvent was removed and the residue was purified by preparative TLC (EtOAc–hexane). The main product (R_f 0.42, 18 mg, 60%) was further purified by crystallization from EtOH, mp 240–242 °C. It was identified as **5** by direct comparison with an authentic sample (mixture melting point, TLC, HPLC, and IR).

Conversion of 8 to 6 (Inversion at C-2). Alcohol 8 (100 mg) and NaOAc (1 g) were refluxed in 50% aqueous EtOH for 40 h. The product was diluted with water, extracted with $CHCl_3$ (4 × 20 ml), washed with water, dried, and evaporated. The residue obtained (92 mg) was resolved by preparative TLC (EtOAc–hexane, 65:35, twice). Two compounds were obtained. The major one was the starting compound (68 mg) and the other (18 mg, 18%), crystallized from $CHCl_3$–MeOH as colorless needles, mp 242–244 °C, was identified as **6** by direct comparison with an authentic sample (mixture melting point, TLC, and IR).

L-Isopodophyllotoxone (12). Alcohol **6** (200 mg) dissolved in pyridine (2 ml) was mixed with CrO_3–pyridine complex[24] (prepared by adding 500 mg of CrO_2 to 5 ml of pyridine), and kept at 25 °C for 20 h. After dilution with water, extraction with $CHCl_3$, washing with water, and subsequent drying and removal of solvent from the extract, the resulting residue out of methanol afforded 160 mg of crystalline **12.** The mother liquor by preparative TLC purification (EtOAc–hexane, 1:1) yielded an additional 18 mg of **12** (total yield 89%). The product was characterized as L-isopodophyllotoxone (**12**): mp 206–208 °C; $[\alpha]_D$ −63.8° (c 0.62, $CHCl_3$); IR ($CHCl_3$) 5.60 (lactone C=O) and 5.92 μ (ketone C=O); UV max (EtOH) 234 nm (ε 4.47), 273 (3.95), and 317 (3.91); NMR (Me_2SO) τ 6.28 (s, 3 H, OMe), 6.24 (s, 6 H, –OMe), 3.92 (s, 2 H, $-OCH_2O$), 3.70 (s, H, C-8), and 3.40 (s, 2 H, C-15, -19), 2.66 (s, H, C-5), the remaining unresolved signals (τ 6.20–5.28) are partly merged with the methoxy group signals; mass spectrum *m/e* 412 (M^+, 100), 397 (28), 367 (25), 337 (10), 297 (12), 168 (46), and 153 (38).

DL-Isopodophyllotoxone (DL-12). Both DL-iso- (DL-**5**) and DL-epiisopodophyllotoxin (DL-**6**) were oxidized and processed similarly to obtain DL-**12** in yields of 68 and 72%, respectively. DL-**12** was sparingly soluble in $CHCl_3$, methanol, and acetone, but could be crystallized from methanol. L-**12** and DL-**12** had identical IR, NMR, and mass spectra, and were indistinguishable by TLC and HPLC.

In an experiment in which DL-**5** was treated with MnO_2 using the conditions reported[4] for its oxidation, the reaction proceeded very slowly. After 8 h at reflux, the product was processed. By preparative TLC 42% of the alcohol was recovered, and 6% of a component having the R_f (TLC) value of authentic DL ketone was obtained. The remainder of the product was a dark brown unidentified mixture.

The oxidation of DL-**6** by use of MnO_2 was also attempted; results were similarly poor.

Acknowledgments. This work was supported in part by USPHS Grant CA-11507. We are indebted to Mr. Lew Cary of Stanford Research Institute (XL-100) and Dr. Richard Sprecher of Memphis State University (CFT-20) for NMR help. Mass spectral determinations were performed by the mass spectrometry laboratory, University of Tennessee.

Registry No.—**5,** 26540-82-9; **5** acetate, 60660-48-2; **6,** 4375-05-7; **7,** 60660-49-3; **7** acetate, 60660-50-6; **8,** 55568-80-4; **12,** 60660-51-7; **16,** 477-52-1.

References and Notes

(1) Part 2 of this series: V. N. Aiyar and F. C. Chang, *J. Org. Chem.*, **40**, 2384 (1975).
(2) L configuration: ref 1, footnote 1.
(3) Part 1 of this series: F. C. Chang, C. Chiang, and V. N. Aiyar, *Phytochemistry*, **14**, 1440 (1975).
(4) W. J. Gensler and F. Johnson, *J. Am. Chem. Soc.*, **85**, 3670 (1963).
(5) E. Schreier, *Helv. Chim. Acta*, **46**, 75 (1963). Dr. Schreier, who reversed the assignment of configuration at C-4 of DL-iso- and epiisopodophyllotoxin on the basis of NMR studies on the epimeric acetates, had obtained the epimeric alcohols through reactions involving the synthetic DL-dihydroxy acids. He did not have access to the Gensler DL-epiisopodophyllotoxin obtained by reduction of the ketone for a direct comparison (private communication from Dr. E. Schreier).

We have repeated the $Zn(BH_4)_2$ reduction of DL-**12** and obtained in low yield a mixture of products (TLC) from which only compound DL-**5** was identifiable. (Dr. Gensler has kindly pointed out that the $Zn(BH_4)_2$ used in his work had been prepared from $NaBH_4$ while ours was derived from $LiBH_4$.) Apparently reduction of complex ketones by mixed metal hydrides is erratic.

$NaBH_4$ in methanol had been used successfully[1] to reduce ketone **9** (2α,3α) to alcohol **8** (2α,3α,4α). Subsequently we have found that ketones **10** and **11** by the same reagent yield alcohols **1** and **3**, respectively, the reported products by $Zn(BH_4)_2$ reduction.[9]

(6) We are indebted to Drs. W. J. Gensler and A. von Wartburg for these reference samples.
(7) J. L. Hartwell and A. W. Schrecker, *Prog. Chem. Org. Nat. Prod.*, **15**, 83 (1958).
(8) E. Schreier, *Helv, Chim. Acta*, **47**, 1520 (1964).
(9) W. J. Gensler, F. Johnson, and A. D. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960).
(10) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **76**, 752 (1954).
(11) The olefin α-apopodophyllotoxin (**15**, 2α), which would be the primary product of dehydration of **7** (or **8**), is unknown. Apparently it is unstable and is promptly isomerized to the β isomer [W. J. Gensler, Q. A. Ahmed, Z. Muljiani, and C. D. Gatsonis, *J. Am. Chem. Soc.*, **93**, 2515 (1970)]. Following the reaction by TLC failed to show a second olefinic product.
(12) Further confirmation was forthcoming when a sample of **7** provided by Dr. von Wartburg proved to be identical with our product by direct comparisons (IR, NMR). The Sandoz compound (unpublished) had been prepared in 1970 by Mr. Max Kuhn (private communication from Dr. von Wartburg).
(13) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **75**, 5916 (1953).
(14) More detailed studies with this and the other diastereomers are in progress. The stability of the lactone ring of **8** is especially interesting in view of the previous observation[1] that it is the one stereoisomer which is cleaved to hydroxy acid under hydrogenolysis conditions (Pd/C).
(15) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. H. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(16) Drs. von Wartburg and E. Schreier in a private communication have confirmed that their manganese dioxide oxidations of DL-**6** to the ketone DL-**12** were "slow and incomplete".
(17) DL-Epiisopodophyllotoxin (DL-**6**) also dissolves poorly in these solvents; probably the poor yield in its oxidation can be attributed to the low solubility. DL-Isosikkomotoxin, which differs from DL-**12** only in having methoxy groups at C-6 and C-7 instead of the 6,7-methylenedioxy group, was oxidized to the corresponding ketone by MnO_2 in 60% yield.[5]
(18) Melting points were determined on an electrical hot stage and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Infracord 137; optical rotation measurements with a Carl Zeiss photoelectric precision polarimeter. Ultraviolet spectra were measured on a Beckman Acta T. M. III spectrometer. Mass spectra were obtained on a Finnegan 1015 GC–MS spectrometer. Nuclear magnetic resonance spectra were done on Varian A-60A, XL-100, or CFT-20 spectrometers, with tetramethylsilane as internal reference; chemical shifts are given on the τ scale.
(19) These signals are temporarily unassigned [see D. C. Ayres, J. A. Harris, P. N. Jenkins, and L. Phillips, *J. Chem. Soc.*, 1343 (1972)].
(20) E. Wiberg and W. Henle, *Z. Naturforsch.*, **76**, 579 (1952).
(21) Epimers **5** and **6** are well resolved by HPLC on a μ-Porasil (Waters Associates) column by methylene chloride–2-propanol (97:3) at a flow rate of 0.7 ml/min.
(22) Based on starting compound consumed.
(23) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **74**, 5676 (1952).
(24) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

A Reinvestigation of the Reaction of α-Pinene with Hypochlorous Acid

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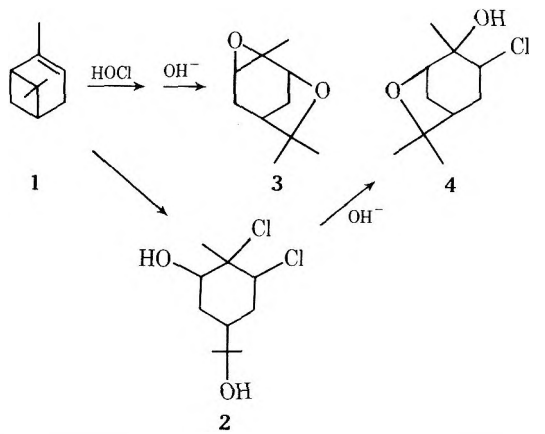
Treatment of α-pinene with hypochlorous acid yields three isomeric *p*-menthane dichlorohydrins **5**, **6**, and **7** in a ratio of 90:5:1, respectively. The structure and stereochemistry of these isomers were established by spectral and chemical means. Treatment of dichlorohydrin **5** with 1 equiv of potassium hydroxide at ambient temperature affords an epoxychlorohydrin **13**. Further reaction of **13** with another equivalent of base at ambient temperature yields a 60:40 mixture of (−)-pinol oxide (**3**) and pinol chlorohydrin (**4**). Epoxide **13** is selectively converted to (−)-pinol oxide (**3**) by reaction with potassium hydroxide at 100 °C or to pinol chlorohydrin (**4**) by reaction with water containing a trace of acid. Zinc and ethanol slowly converts pinol chlorohydrin (**4**) into (+)-pinol (**14**) which is epoxidized to (+)-pinol oxide (**3**), the enantiomer of (−)-pinol oxide (**3**) obtained by the action of alkali on **5**.

α-Pinene (**1**) is known to react with 2 equiv of hypochlorous acid[2-4] to afford, among other products, an optically active dichlorohydrin **2**, mp 136–137 °C. The action of alkali on

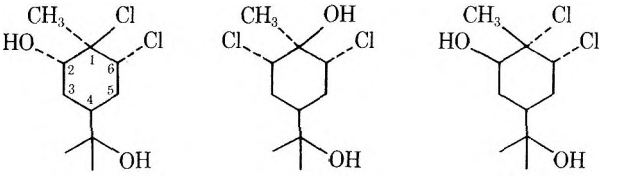


1 3 4

2

dichlorohydrin **2** or on the crude mixture obtained from hypochlorous acid and α-pinene gave pinol oxide (**3**)[5] and optically active, mp 131–132 °C, and racemic, mp 104–105 °C, pinol chlorohydrin (**4**). Assignment of stereochemistry to these materials based on the evidence provided in the literature is not possible. Moreover, a number of the confusing observations made by Wagner[2] and Henderson[3] can be traced to their use of α-pinene which was of questionable optical purity[7] and contained β-pinene.

Our need for a sample of optically active pinol oxide (**3**) prompted us to reinvestigate the action of hypochlorous acid on (+)-α-pinene.[8] We observed that the procedure of Wagner[2] involving the addition of a sodium hypochlorite solution to acetic acid and α-pinene led to a complicated mixture of products. We then turned to the procedure of Henderson and Marsh[3] using a distilled solution of hypochlorous acid prepared from calcium hypochlorite and boric acid[10] and in this way obtained three isomeric *p*-menthane dichlorohydrins **5**, **6**, and **7** in a ratio of 90:5:1, respectively.

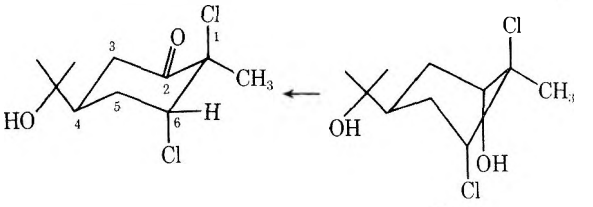


5 (90%) **6** (5%) **7** (1%)

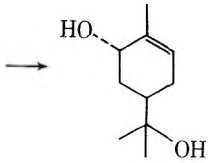
The major product **5** partially crystallized from the crude mixture. The remainder of the mixture was subjected to column chromatography affording additional quantities of pure **5** as well the two minor isomers **6** and **7**, both of which were still contaminated with **5**.

With pure dichlorohydrin **5** in hand an investigation of its structure and stereochemistry was undertaken. The most significant feature of its NMR spectrum was a methyl singlet at 1.76 ppm assigned to the methyl group at C-1 which must be attached to a carbon bearing a chlorine atom. The reaction of dichlorohydrin **5** with zinc and ethanol afforded *trans*-sobrerol (**8**),[11] which establishes a trans relationship between the C-2 hydroxyl group and the C-4 hydroxyisopropyl group in **5**.

Oxidation of **5** with Jones reagent gave the dichlorohydroxycarvone derivative **9**.[12] A triplet at 4.60 ppm with a



9 **5a**



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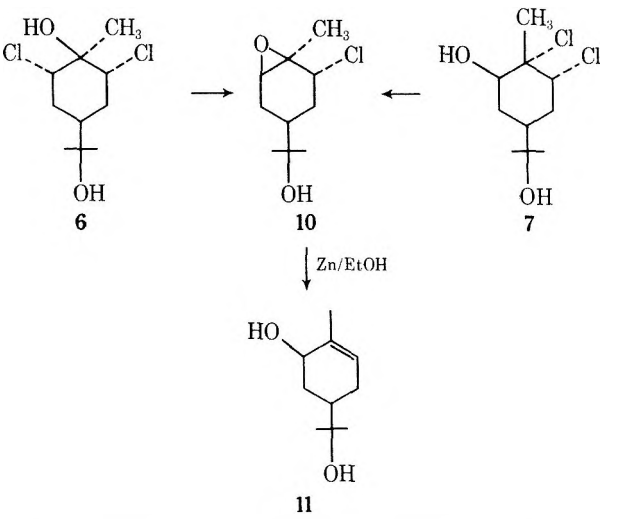
coupling constant of 2.5 Hz[13] suggested the presence of an equatorial proton at C-6. An equatorial methyl and axial chlorine at C-1 were demonstrated by a small upfield shift of the methyl signal at 1.75 ppm on changing from deuteriochloroform to benzene,[14] by an infrared carbonyl absorption at 5.80 μ which is essentially identical with the carbonyl absorption exhibited by carvomenthone (5.82 μ),[15] and by an ultraviolet maximum at 302 nm (ϵ 40) which is markedly shifted to higher wavelength[16] from the maximum at 286 nm shown by carvomenthone. Thus, the geometry of the two chlorines in **9** must be trans and the dichlorohydrin from which it is derived must have the structure, stereochemistry, and conformation depicted by **5a**.

The inability to cleanly separate dichlorohydrins **6** and **7** from **5** prevented a direct determination of their structure and stereochemistry. However, inspection of the NMR spectrum of an 80:20 mixture of **6** and **5** revealed a sharp singlet at 1.50 ppm assigned to a CH_3CO group at C-1 and a clean quartet at 4.37 ppm which was the only downfield signal attributed to **6**. The symmetric nature of the latter signal suggested a symmetric structure for **6** and if this were indeed the case, then **6** must be optically inactive. There was no way to ascertain this fact directly because the mixture showed low optical rotation values presumedly attributed to the presence of **5**. This matter was resolved by treating the mixture of **6** and **5** with potassium carbonate in aqueous methanol, which led to an easily separated mixture of epoxychlorohydrin **10** and pinol oxide (**3**) and pinol chlorohydrin (**4**) which are derived from dichlorohydrin **5** (see below). Epoxide **10** proved to be optically inactive and requires that its precursor be dichlorohydrin **6**.[17] Treatment of epoxide **10** with zinc and aqueous ethanol afforded *dl-cis*-sobrerol (**11**),[11] which further established the geometric relationship of the functional groups in **10** and **6**.

The problems encountered with the separation of **7** from **5** were much the same experienced with **6**. When treated with potassium carbonate in aqueous methanol the mixture of **7** and **5** yielded the same three products, **3**, **4**, and **10**, obtained from the mixture of **6** and **5**. In this instance, however, the epoxychlorohydrin **10** proved to be optically active requiring its precursor to be formulated as structure **7**.

It may be noted that the three dichlorohydrins **5**, **6**, and **7**



6 **10** **7**

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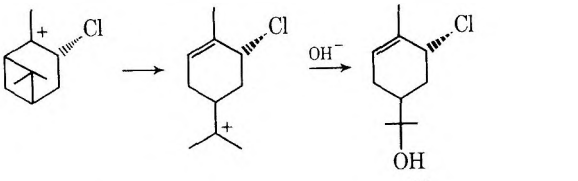
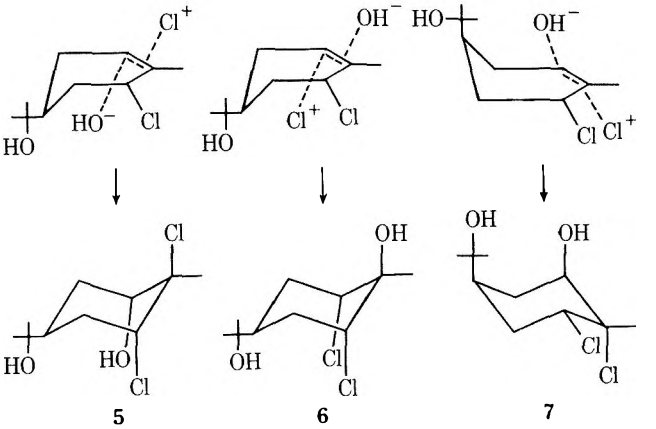
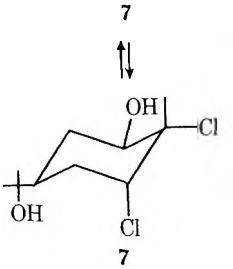
have the same stereochemistry at C-6 suggesting that they are formed from a common intermediate which is generated by initial attack of chloronium ion from the least hindered side at the C-2 position of α-pinene (**1**). Ring opening and capture of hydroxide ion would convert intermediate **1a** into the unsaturated chlorohydrin **12**.[18] Anti-diaxial addition of the second hypochlorous acid molecule to **12** is apparently initiated to the greatest extent by a chloronium ion approaching from the least hindered side of the carbon–carbon double bond, i.e., trans to the chlorine at C-6, to form dichlorohydrin **5**. The predominant formation of this seemingly anti-Markownikoff product[20] may also be a consequence of the inductive effect of the chlorine at C-6 since it is known that addition of hypochlorous acid to allyl chloride gives predominantly 2,3-dichloro-1-propanol.[22] Formation of the minor isomers **6** and **7** is a consequence of chlorine attack on **12** from the more hindered side with overall anti-diaxial addition leading to **6**. The very small amount of **7** may result from



12



5 **6** **7**



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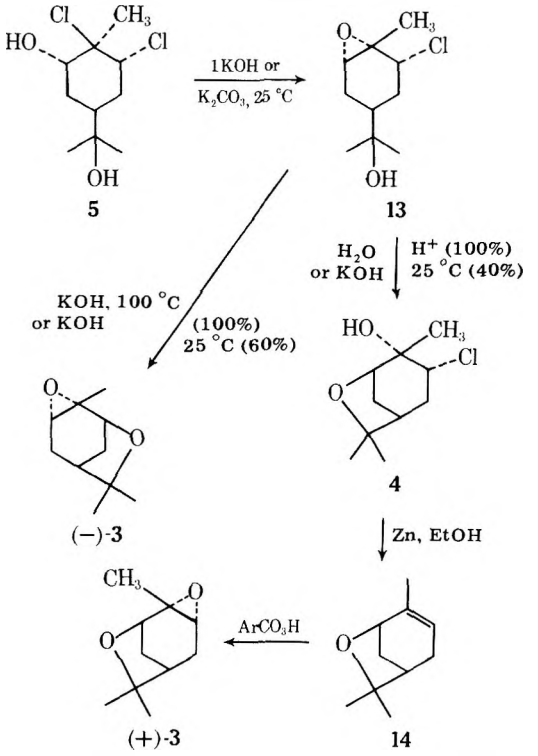
diaxial addition to a less stable conformation of **12** or some other obscure mechanism.

An investigation of the action of bases on dichlorohydrin **5** revealed that several products are formed depending on reaction conditions. Treatment of **5** with 2 equiv of potassium hydroxide in water at reflux gave a high yield of pinol oxide (**3**) containing a trace of pinol chlorohydrin (**4**). When the same reaction was conducted at ambient temperature a 60:40 mixture of **3** and **4** was obtained. With 1 equiv of base at ambient temperature the epoxychlorohydrin **13** was the only

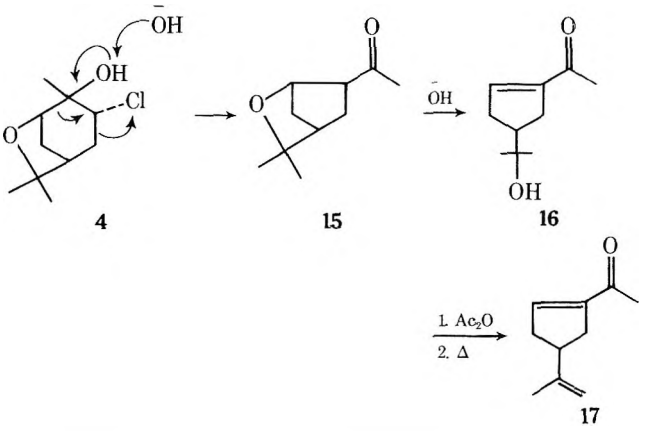


product. Epoxychlorohydrin **13** is the precursor for both **3** and **4** since it is converted to pinol oxide **3** in high yield when treated with 1 equiv of base at reflux and gives a 60:40 mixture of **3** and **4** when the reaction is conducted at ambient temperature. When **13** was kept in water containing a trace of acid it was quantitatively transformed into pinol chlorohydrin (**4**).[23]

The structure of pinol chlorohydrin (**4**) was demonstrated by an NMR methyl singlet at 1.36 ppm which indicates the compound is a tertiary alcohol. The large coupling constant exhibited by the quartet at 4.32 ppm suggests that the C-3 proton is axial and the chlorine equatorial. The cis relationship of the chlorohydrin is in accord with the observation that **4** is recovered unchanged after exposure to base at ambient temperature.[2,5] Prolonged heating of **4** with zinc and ethanol gave (+)-pinol (**14**) which on epoxidation with *m*-chloroperbenzoic acid afforded (+)-pinol oxide (**3**), $[\alpha]_D$ +32.24°, the enantiomer of (−)-pinol oxide (**3**), $[\alpha]_D$ −32.06°, obtained by the action of base on dichlorohydrin **5**.

It is instructive to note that the pinol skeletons of **3** and **4** are enantiomeric. This is expected if the action of base on epoxychlorohydrin **13** proceeds by way of an intramolecular alkoxide displacement of epoxy oxygen or chloride. Since the conversion of **13** can be controlled to yield either **3** or **4** and since **13** is readily prepared from (+)-α-pinene, (+)-α-pinene becomes a convenient starting material for the synthesis of both pure enantionmers of pinol oxide (**3**).

One final reaction of pinol chlorohydrin (**4**) is worthy of comment. Treatment of **4** with aqueous potassium hydroxide at reflux afforded the acetylcyclopentene derivative **16** whose structure was confirmed by acetylation and pyrolysis to 1-



acetyl-4-isopropenylcyclopentene (**17**).[24] A quasi-benzylic acid type of rearrangement[25] of **4** would yield **15** which then undergoes a base-initiated elimination to afford the acetylcyclopentene **16**.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Infracord, Model 137-B. NMR spectra were recorded with Varian Associates A-60A and Perkin-Elmer R-32 instruments and are reported in parts per million from tetramethylsilane as an internal standard. Optical rotations were measured with a Zeiss polarimeter. Mass spectra were determined on a Hitachi RMU-6D instrument by the Purdue University Spectral Service. Ultraviolet spectra were recorded on a Cary Model 15 instrument. Microanalyses were performed by Dr. C. S. Yeh and associates.

Reaction of (+)-(1*R*,5*R*)-α-Pinene with Hypochlorous Acid. To 5 ml (0.31 mol) of (+)-α-pinene was added dropwise with vigorous stirring (30 min) 850 ml (0.028 mol) of 0.033 M hypochlorous acid solution.[10] The mixture was extracted with 25 ml of pentane. The pentane solution was dried (Na_2SO_4) and evaporated to leave 2.72 g of pure α-pinene. The aqueous phase was saturated with sodium chloride and extracted with ether. The ether solution was dried (Na_2SO_4) and the ether removed to leave 2.67 g of a viscous light yellow oil which gradually deposited crystals on standing. The mixture was diluted with carbon tetrachloride and the solid separated by filtration. Extensive column chromatography of the carbon tetrachloride solution on silica gel using ether–pentane as eluent gave additional quantities of the pure major product **5** and fractions rich in two minor components **6** and **7** which could not be freed entirely from the major product. The proportion of **5**, **6**, and **7** (90:5:1) was estimated by examining the NMR spectra of the crude product and various chromatography fractions.

Pure (1*R*,2*S*,4*S*,6*R*)-1-*cis*-6-dichloro-*trans*-*p*-menthane-*cis*-2,8-diol (**5**) was obtained by recrystallization from carbon tetrachloride and showed mp 134–135 °C; $[\alpha]^{26}_D$ −15.05° (c 3.76, $CHCl_3$); IR ($CHCl_3$) 2.80 and 2.90 μ; NMR ($CDCl_3$) 1.21 [s, 6, $(CH_3)_2C$], 1.76 (s, 3, CH_3CCl), 1.8–2.4 (m, 5), 2.66 (2, –OH), 4.02 (m, 1, –CHO), and 4.46 ppm (m, 1, –CHCl); mass spectrum *m/e* (rel intensity) 225 (1), 207 (3), 187 (3), 93 (18), 59 (100), 43 (35), 41 (13), and 39 (7).

Conversion of Dichlorohydrin 5 to *trans*-Sobrerol (8) with Zinc and Ethanol. A mixture of 863 mg (0.036 mol) of **5**, 2.5 g (0.038 g-atom) of acid-washed zinc dust, 20 ml of 95% ethanol, and 5 ml of water was refluxed for 18 h. The mixture was cooled, diluted with 50 ml of water, saturated with sodium chloride, and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated to give 536 mg of white solid. Recrystallization from ethyl acetate gave pure *trans*-sobrerol (**8**): mp 148–149 °C (lit.[11] mp 148–149 °C); NMR ($CDCl_3$) 1.20 [s, 6, $(CH_3)_2C$–], 1.3–2.3 (m, 7), 1.79 (s, 3, CH_3C=C–), 4.04 (m, 1, CHO) and 5.5 ppm (m, CH=C–); mass spectrum *m/e* (rel intensity) 170 (2), 152 (28), 137 (25), 110 (12), 109 (85), 108 (14), 95 (21), 94 (18), 93 (16), 81 (19), 79 (50), 71 (12), 69 (17), 59 (100), 55 (21), 43 (77), 41 (37), and 39 (21).

(1*R*,4*S*,6*R*)-1-*cis*-6-Dichloro-8-hydroxy-*trans*-*p*-menthan-2-one (9). Approximately 1 ml of Jones reagent was added to a vigorously stirred solution of 400 mg (0.0017 mol) of **5** in 25 ml of acetone at 0 °C. Isopropyl alcohol was added to destroy the excess oxidant and ether was added. The salts were removed and washed with ether. The ether solution was washed with water and dried ($MgSO_4$) and the ether was removed to yield 356 mg of an oil. Pure **9** obtained by TLC could not be induced to crystallize and showed $[\alpha]^{25}_D$ +39.56° (c 3.20,

$CHCl_3$); IR 2.95 and 5.80 μ; NMR ($CDCl_3$) 1.25 [s, 6, $(CH_3)_2C$–], 1.75 (s, 3, CH_3CCl), 2.0–3.1 (m, 6), and 4.60 ppm (t, 1, J = 2.5 Hz, –CHCl); NMR (C_6H_6) 1.00 [s, 6, $(CH_3)_2C$–], 1.72 (s, 3, CH_3CCl), and 4.29 ppm (t, 1, –CHCl); mass spectrum m/e (rel intensity) 238 (1), 223 (3), 145 (9), 109 (31), 59 (84), 43 (100), 41 (21), and 39 (14).

Anal. Calcd for $C_{10}H_{16}Cl_2O_2$: C, 50.21; H, 6.69; Cl, 29.71. Found: C, 50.50; H, 6.91; Cl, 29.63.

Reaction of a Mixture of 5 and 6 with Potassium Carbonate. A solution of 2 g of a 2:1 mixture of **5** and **6** and 3 g of potassium carbonate in 20 ml of methanol and 10 ml of water was refluxed for 4 h. The solution was taken up in ether which was then washed with water and dried (Na_2SO_4). Removal of the solvent left 1.4 g of a brown oil. Column chromatography of the oil on silica gel using ether–pentane as an eluent gave 570 mg of pinol oxide (**3**), 90 mg of pinol chlorohydrin (**4**), and 448 mg of *cis*-6-chloro-1,2-epoxy-*trans*-*p*-methan-8-ol (**10**): $[\alpha]^{29}D$ 0° (*c* 6.40, $CHCl_3$); IR 2.93, 3.43, 6.70, 6.94, 7.25, 7.32, 7.66, 7.82, 7.97, 8.10, 8.24, 8.75, 8.95, 9.16, 9.45, 9.81, 10.20, 10.42, 10.61, 10.76, 10.88, 11.34, 11.82, 12.20, 13.13, and 14.1–14.5 μ; NMR ($CDCl_3$) 1.15 [s, 6, $(CH_3)_2C$–], 1.47 (s, 3, CH_3CO), 1.7–2.3 (m, 5), 3.14 (d, 1, CHO–), and 4.43 ppm (t, 1, –CHCl); mass spectrum m/e (rel intensity) 204 (1), 151 (5), 111 (10), 109 (15), 107 (13), 105 (16), 95 (10), 93 (34), 84 (12), 81 (10), 71 (17), 69 (12), 67 (10), 59 (100), 55 (11), 53 (11), 43 (98), 41 (29), and 39 (22).

When the reaction of the mixture of **5** and **6** with potassium carbonate was conducted at ambient temperature the NMR spectrum of the crude product indicated a mixture of epoxide **10** and epoxide **13**.

Conversion of Epoxide 10 to (±)-*cis*-Sobrerol with Zinc and Ethanol. A mixture of 223 mg (0.0011 mol) of epoxide **10**, 0.5 g (0.0076 g-atom) of acid-washed zinc, 26 ml of ethanol, and 5 ml of water was kept at reflux for 70 h. Saturated ammonium chloride solution (15 ml) was added and the resulting solution was saturated with sodium chloride. The solution was extracted with ether, and the ether was dried (Na_2SO_4) and removed to yield 148 mg of a light yellow oil which slowly crystallized. The solid was washed with ether to give 82 mg of (±)-*cis*-sobrerol (**11**): mp 103–104 °C (lit.[11] mp 105–106 °C); NMR ($CDCl_3$) 1.18 [s, 6, $(CH_3)_2C$–], 1.3–2.5 (m, 7), 1.75 (s, 3, $CH_3C{=}C$–), 4.12 (m, 1, –CHO), and 5.47 ppm (m, 1, –CH=C–); mass spectrum m/e (rel intensity) 170 (1), 152 (24), 137 (34), 109 (69), 95 (22), 94 (78), 93 (38), 91 (15), 79 (68), 77 (17), 69 (21), 59 (100), 55 (22), 43 (74), 41 (30), and 39 (17).

Reaction of a Mixture of 5 and 7 with Potassium Carbonate. A solution of 350 mg (0.0015 mol) of a 55:45 mixture of **7** and **5**, 0.5 g (0.0036 mol) of potassium carbonate, 25 ml of methanol, and 3 ml of water was kept at reflux for 2.5 h. Workup in the usual manner gave 286 mg of a brown oil. Preparative TLC of this oil afforded 46 mg of pinol oxide (**3**), 11 mg of pinol chlorohydrin (**4**), and 133 mg of (1*R*,2*R*,4*S*,6*R*)-*cis*-6-chloro-1,2-epoxy-*trans*-*p*-menthan-8-ol (**10**). An analytical sample of (+)-**10** was obtained by recrystallization from ethyl acetate and showed mp 46–47 °C, $[\alpha]^{26}D$ +72.62° (*c* 2.40, $CHCl_3$), and IR and NMR spectra identical with those of (±)-**10** described above.

Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.31; Cl, 17.36. Found: C, 58.50; H, 8.34; Cl, 17.50.

Reaction of Dichlorohydrin 5 with Excess Potassium Hydroxide at 100 °C. A mixture of 14 g (0.058 mol) of **5**, 40 ml (0.142 mol) of 20% potassium hydroxide, and 100 ml of water was heated to reflux for 1 h. The mixture was extracted with ether, and the ether was dried (Na_2SO_4) and evaporated to leave 9.1 g of brown oil whose NMR spectrum indicated it to be pinol oxide (**3**) containing a small amount of pinol chlorohydrin (**4**). Two distillations in vacuo afforded 6.8 g of pure (−)-pinol oxide (**3**): $[\alpha]^{27}D$ −32.06 (*c* 4.32, $CHCl_3$); NMR ($CDCl_3$) 1.18 and 1.28 [s, 6, $(CH_3)_2C$–], 1.36 (s, 3, CH_3CO–), 1.7–2.2 (m, 5), 2.87 (d, –CH–O–C–), and 4.17 ppm 1, (d, 1, –CHO).

Reaction of Excess Potassium Hydroxide with Dichlorohydrin 5 at Ambient Temperature. A mixture of 1.2 g (50 mmol) of **5**, 5 ml (178 mmol) of 20% potassium hydroxide, and 10 ml of water was stirred at ambient temperature for 16 h. The mixture was extracted with ether, and the ether was then dried and removed to yield 810 mg of a light brown oil. NMR analysis revealed the presence of 60% of pinol oxide (**3**) and 40% of pinol chlorohydrin (**4**). Upon standing the oil partially crystallized. The solid was separated and recrystallized from hexane to give 285 mg of pure **4**: mp 130–131 °C; NMR ($CDCl_3$) 1.19 and 1.29 [s, 6, $(CH_3)_2C$–], 1.7–2.5 (m, 6), 4.04 (d, 1, CHOC), and 4.32 ppm (q, 1, –CHCl), mass spectrum m/e (rel intensity) 204 (2), 168 (12), 140 (18), 125 (22), 109 (16), 107 (20), 98 (18), 97 (60), 83 (12), 82 (25), 81 (13), 71 (73), 70 (17), 69 (39), 67 (10), 55 (15), 43 (100), 41 (38), and 39 (22).

Reaction of 1 Equiv of Potassium Hydroxide with Dichlorohydrin 5 at Ambient Temperature. A mixture of 350 mg (14 mmol) of **5**, 0.5 ml (15 mmol) of 20% potassium hydroxide, and 20 ml of water was stirred at ambient temperature for 1 h. The usual workup gave 241 mg of a light yellow oil. TLC on silica gel using pentane–acetone–ethyl acetate gave 188 mg of pure (1*S*,2*S*,4*S*,6*R*)-*trans*-6-chloro-1,2-epoxy-*cis*-*p*-menthan-8-ol (**13**): $[\alpha]^{25}D$ +24.36° (*c* 2.34, $CHCl_3$); IR 2.93, 3.40, 6.91, 7.25, 7.82, 8.09, 8.27, 8.58, 8.75, 9.02, 9.25, 9.69, 9.90, 10.60, 11.39, 11.89, 12.21, 12.83, 13.60, and 14.20 μ; NMR ($CDCl_3$) 1.19 [s, 6, $(CH_3)_2C$–], 1.42 (s, 3, CH_3–C–O–C), 3.30 (d, 1, –CH–O–C), and 4.45 ppm (m, 1, –CHCl); mass spectrum m/e (rel intensity) 204 (1), 125 (13), 111 (10), 109 (16), 107 (15), 105 (10), 97 (14), 95 (11), 93 (15), 81 (12), 71 (21), 69 (20), 67 (10), 59 (79), 55 (13), 43 (100), 41 (28), and 39 (18).

Reactions of Epoxychlorohydrin 13. A. Potassium Hydroxide at Reflux. When a mixture of 70 mg of **13** was heated at reflux for 4.5 h with 0.2 ml of 20% potassium hydroxide and 10 ml of water there was obtained 49 mg of an oil whose NMR spectrum indicated that it was relatively pure pinol oxide (**3**).

B. Potassium Hydroxide at Ambient Temperature. A mixture of 240 mg of **13**, 0.4 ml of 20% potassium hydroxide, and 10 ml of water was stirred at ambient temperature for 16 h. The usual workup gave 189 mg of an oil whose NMR indicated the presence of 60% of pinol oxide (**3**) and 40% of pinol chlorohydrin (**4**).

C. Water and Catalytic Amount of Acid. A mixture of 197 mg of **13** was stirred with 10 ml of water containing 3 drops of 20% sulfuric acid at ambient temperature for 18 h. The usual workup gave 181 mg of white solid. Recrystallization from hexane afforded pure (−)-pinol chlorohydrin (**4**), mp 130–131 °C, $[\alpha]^{26}D$ −134.86° (*c* 1.4, $CHCl_3$).

When a 140-mg sample of **13** was stirred with water for 18 h, there was obtained 122 mg of **4**. When another sample of **16** was stirred with freshly distilled and degassed water under a nitrogen atmosphere, the sample of **13** was recovered unchanged.

(1*R*,5*R*)-(+)-Pinol (14). A mixture of 5.65 g (0.0276 mol) of (−)-pinol chlorohydrin (**4**), 5 g (0.0765 g-atom) of acid-washed zinc, 200 ml of ethanol, and 50 ml of water was heated at reflux for 16 days. Approximately 10 ml of ethanol was added each day to compensate for evaporative loss. After 2% hydrochloric acid was added the mixture was extracted with pentane. The pentane extracts were washed with 5% sodium bicarbonate solution and dried (Na_2SO_4), and the pentane was removed to leave 3.9 g of a colorless oil. The NMR spectrum of the oil revealed the presence of pinol contaminated with approximately 33% of pinol chlorohydrin (**4**). The pinol chlorohydrin (**4**) slowly crystallized from the oil and after 5 days the liquid portion was removed by a pipet and the solid washed with pentane. The combined liquid and pentane washings were distilled to afford 1.08 g of pure (+)-pinol (**14**), bp 25–29 °C (0.2 mm), $[\alpha]^{25}D$ +80.7° (*c* 3.0, $CHCl_3$).

(1*S*,3*R*,4*S*,5*R*)-*trans*-Pinol Oxide (3). A solution of 0.5 g of (+)-pinol (**14**) and 1 g of *m*-chloroperbenzoic acid in 40 ml of methylene chloride was stirred at ambient temperature for 48 h. The solution was taken up in ether and washed with saturated sodium bisulfite solution, 5% sodium bicarbonate solution, and water. The solution was dried (Na_2SO_4) and distilled to yield 456 mg of (+)-pinol oxide (**3**), bp 34–35 °C (0.3 mm), $[\alpha]^{26}D$ +32.24° (*c* 4.68, $CHCl_3$).

Reaction of Pinol Chlorohydrin (4) with Potassium Hydroxide. A mixture of 428 mg (21 mmol) of **4**, 1 ml (30 mmol) of 20% potassium hydroxide, and 10 ml of water was heated at reflux for 2 h. The mixture was extracted with ether, the ether fractions were dried (Na_2SO_4), and the ether was removed to give 276 mg of yellow oil. Preparative TLC of the oil on silica gel using pentane–ether–ethyl acetate yielded 152 mg of (4*S*)-1-acetyl-4-(1-hydroxy-1-methylethyl)cyclopentene (**16**): $[\alpha]^{26}D$ −13.8° (*c* 1.0, $CHCl_3$); IR 2.92, 5.87, 6.03, and 6.17 μ; NMR ($CDCl_3$) 1.19 [s, 6, $(CH_3)_2C$–], 1.5–2.2 (m, 2), 2.30 (s, 3, CH_3CO–), 2.45–2.80 (m, 4), and 6.68 ppm (m, 1, –CH=C–); mass spectrum m/e (rel intensity) 168 (2), 153 (6), 150 (15), 135 (14), 110 (40), 109 (16), 107 (12), 95 (23), 93 (12), 69 (12), 67 (33), 66 (14), 59 (45), 43 (100), 41 (16), and 39 (15).

A solution of 243 mg of **16** in 10 ml of acetic anhydride was heated at reflux for 5 h. The solution was poured into 100 ml of water and solid sodium bicarbonate was added until evolution of carbon dioxide ceased. The solution was extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated to leave 278 mg of a clear oil whose NMR confirmed the formation of the acetate derivative of **16**. The acetate was injected into a gas chromatograph with the injector block at 400 °C (10% SE-30 column at 150 °C) and (4*S*)-1-acetyl-4-isopropenylcyclopentene (**17**) was collected and displayed IR and NMR spectra identical with those of an authentic sample.[24] The 2,4-dinitrophenylhydrazone derivative of **17** was recrystallized from ethanol as dark red plates and showed mp 180–181 °C (lit. mp 178–180 °C).

Registry No.—**1**, 7785-70-8; (−)-**3**, 56142-60-0; (+)-**3**, 56142-61-1;

4, 60661-94-1; 5, 60661-95-2; 6, 60661-96-3; 7, 60686-99-9; 8, 38235-58-4; 9, 60661-97-4; (+)-10, 60661-98-5; (±)-10, 60687-02-7; 11, 60687-00-5; 13, 60687-01-6; 14, 55822-06-5; 16, 60661-99-6; hypochlorous acid, 7790-92-3; zinc, 7440-66-6; ethanol, 64-17-5; potassium carbonate, 584-08-7; potassium hydroxide, 1310-58-3.

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Pinol Derivatives from Lithium Aluminum Hydride Reduction of Cineole Chlorohydrin

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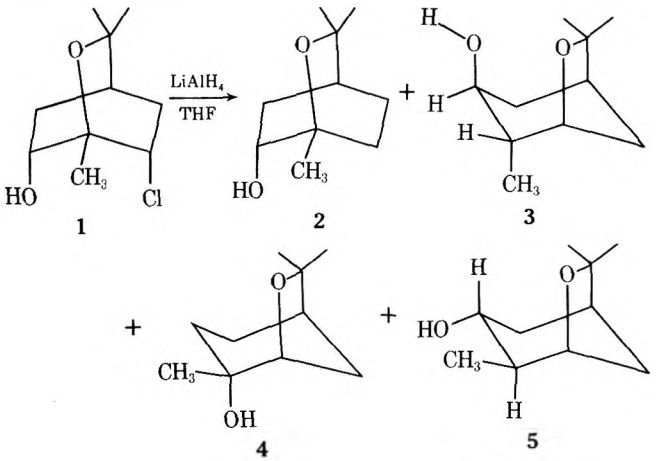
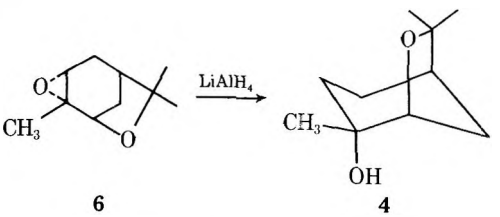
Lithium aluminum hydride reduction of (±)-*endo*-6-hydroxy-*endo*-7-chlorocineole (1) affords *cis*-3-hydroxy-*trans*-dihydropinol (3, 50%), *trans*-4-hydroxydihydropinol (4, 32%), *trans*-3-hydroxy-*cis*-dihydropinol (5, 11%), and *endo*-6-hydroxycineole (2, 5%). It is shown that treatment of chlorohydrin 1 with 1 equiv of hydride leads predominantly, via intermediate 14 followed by an oxygen and chlorine shift, to a pinol chlorohydrin derivative 17 which then loses chloride ion accompanied by a hydride shift to afford *trans*-dihydropinol-3-one (12). Ketone 12 is reduced from the least hindered side to give alcohol 3. A competing process transforms intermediate 14 into pinol oxide (6) which is then reduced to alcohol 4. Intermediate 14, and possibly 17, also affords small amounts of alcohol 5.

A sample of *endo*-6-hydroxycineole (2) was desired in connection with our studies of the chemistry of pinol.[2] It was envisioned that lithium aluminum hydride reduction of (±)-*endo*-6-hydroxy-*endo*-7-chlorocineole (1)[2] would provide



a route for its preparation. However, vapor phase chromatographic analysis of the reduction product indicated the formation of a mixture comprised of four major components: *cis*-3-hydroxy-*trans*-dihydropinol (3, 50%), *trans*-4-hydroxydihydropinol (4, 32%),[3] *trans*-3-hydroxy-*cis*-dihydropinol (5, 11%), and *endo*-6-hydroxycineole (2, 5%). This publication is concerned with the evidence on which the assignment of these structures is based and the mechanism by which these compounds are formed.

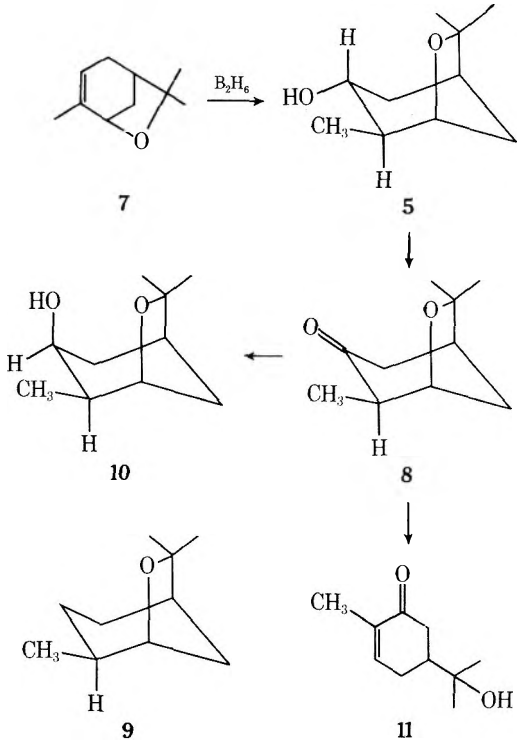
The tertiary alcohol 4 was characterized by its NMR spectrum which showed, in part, methyl singlets at δ 1.23 and 1.37 ppm and a one-proton doublet at 3.82 ppm attributed to the bridgehead hydrogen of a pinol derivative. The structure of 4 was confirmed by comparison with an authentic sample prepared by lithium aluminum hydride reduction of (±)-pinol oxide (6).[4]



Complete characterization of 2 was not possible because of a lack of sufficient material. However, its infrared spectrum in solution showed hydroxyl absorption at 2.78 and 2.89 μ, while its CAT improved NMR spectrum displayed methyl singlets at 1.14, 1.27, and 1.34 ppm and a one-proton quartet ($W_{1/2}$ = 20 Hz) at 3.55 ppm whose chemical shift and multi-

plicity are consistent with the assignment of an exo proton at C-6 in an oxabicyclo[2.2.2]octane ring system.

The NMR spectrum of **5** exhibited methyl singlets at 1.19 and 1.33 ppm and a methyl doublet at 1.09 ppm. A characteristic pinol bridgehead proton doublet was observed at 3.80 ppm, while a quartet at 3.62 ppm with a $W_{1/2}$ of 26 Hz indicated that the proton at C-3 was axial. This structural assignment was confirmed by an independent synthesis of **5** involving the hydroboration of (±)-pinol (**7**).

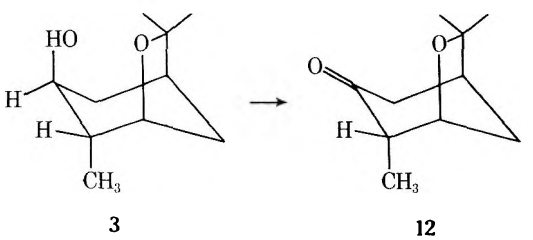


Oxidation of **5** according to the Jones procedure gave a single ketone **8**. An equatorial methyl group in **8** was indicated by the small (6 Hz) downfield NMR shift of the methyl signal when the solvent was changed from deuteriochloroform to benzene.[5] The appearance of a doublet for the C-5 bridgehead proton lends additional support for this conclusion. The dihedral angles between the axial protons at C-4 and C-8 and the quasi-equatorial proton at C-5 are approximately 90° resulting in small or negligible spin–spin coupling; consequently, a doublet results from exclusive spin coupling between the C-5 proton and the equatorial C-8 proton. *cis*-Dihydropinol (**9**) similarly shows a doublet for its C-5 bridgehead proton.

Lithium aluminum hydride reduction of ketone **8** affords alcohol **10** and only a small amount of alcohol **5** suggesting that hydride reduction occurs predominantly from the least hindered side of the molecule. The small coupling constant ($W_{1/2}$ = 13 Hz) for the C-3 proton in alcohol **10** is in accord with its equatorial assignment.

An attempt to epimerize ketone **8** with sodium methoxide in methanol failed since the ketone underwent an elimination reaction to carvone hydrate (**11**).[2,6]

Oxidation of **3** according to the Jones procedure gave ketone **12**. Axial methyl groups in **3** and **12** were indicated by a multiplet for the C-5 bridgehead proton in both compounds, and by an 18.6-Hz upfield shift of the C-4 methyl group in **12** when its NMR spectrum was determined in benzene.[5] Inspection of molecular models of these compounds indicate that the dihedral angle between the C-5 and C-4β and C-8β protons in approximately 30°; consequently, the C-5 proton should spin couple with both C-4β and C-8β protons giving rise to the observed multiplet. A small coupling constant indicated the presence of an equatorial C-3 proton in **3** which was further confirmed by a downfield shift of one of the *gem*-dimethyl groups to 1.54 ppm owing to the proximity of the axial hydroxyl group at C-3.



We now turn to a consideration of the intermediates involved in the lithium aluminum hydride reduction of **1** which results in the formation of a major product **3** where C-3 and C-5 have inverted configurations and C-4 has retained configuration. The first step in the reduction of **1** must involve the reaction of the alcohol group to afford intermediate **13**. Ionization of chloride, possibly assisted by an electrophilic aluminum species and/or neighboring oxygen, generates cation **14** (or its classical counterparts). The cation may be attacked by hydride, most likely in an intramolecular fashion,[7] to yield alcohol **5**, or by oxygen at C-6 to give pinol oxide (**6**), which is then reduced by lithium aluminum hydride to alcohol **4**. In connection with the latter conversion it is instructive to note that pinol oxide (**6**) is formed in high yield when cineole chlorohydrin (**1**) is treated with sodium hydroxide[2] or sodium hydride. Alcohol **3** forms as a consequence of a hydride shift from C-6 to give ketone **12** which is then reduced by hydride from the least hindered side of the molecule. The difficulty with accepting the proposal of the intermediacy of **14** in the formation of **3** is the requirement of a hydride ion migration which is syn to the oxygen which migrates from C-1 to C-7 of the cineole ring.

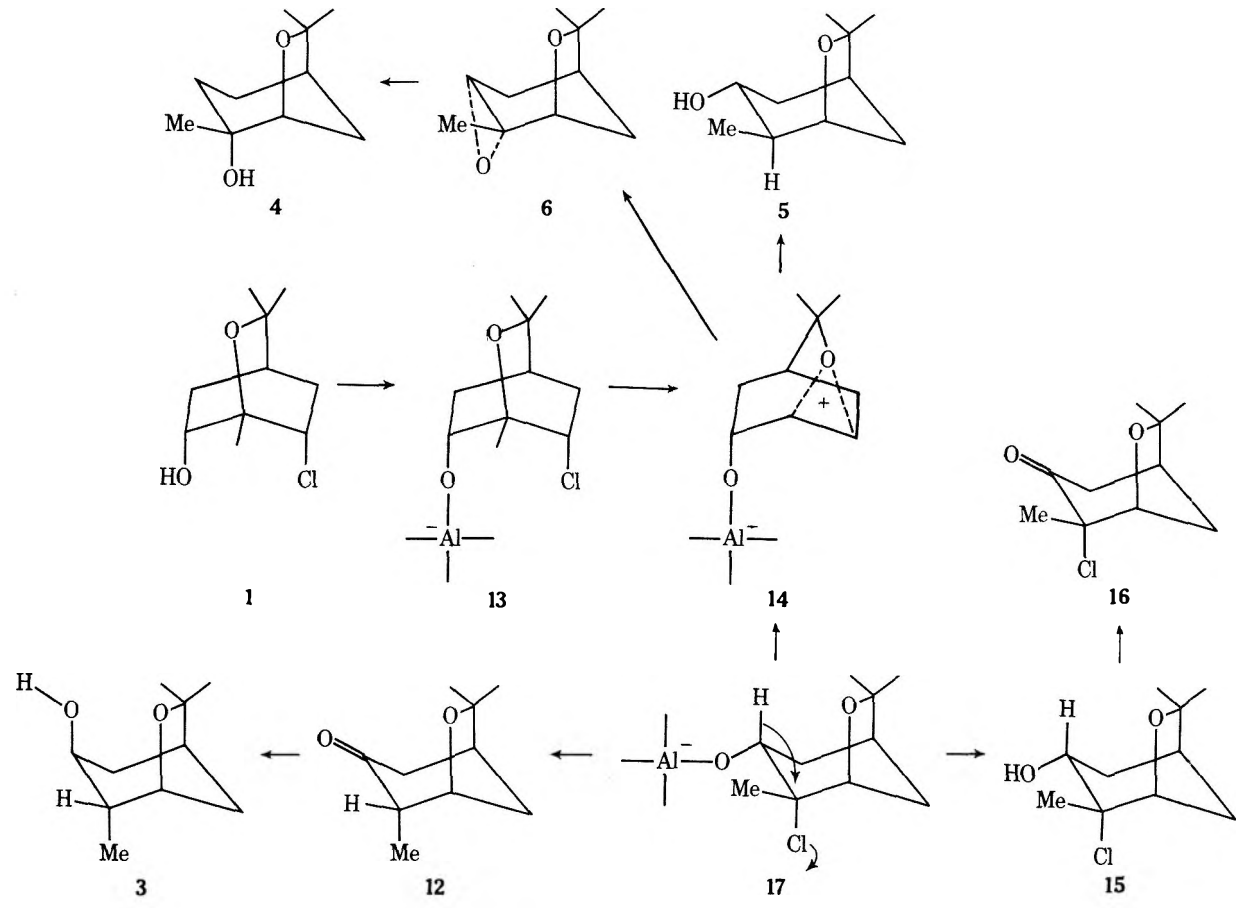
This matter was clarified when it was observed that the action of 1 equiv of hydride on chlorohydrin **1** gave little, if any, of the products obtained with excess hydride and instead yielded a mixture of starting chlorohydrin **1**, pinol chlorohydrin (**15**), and small amounts of pinol oxide (**6**) and ketone **12**.

Pinol chlorohydrin (**15**) displayed a large coupling constant for the C-3 proton indicating it to be axial. The configuration of the chlorine in **15** was established by examining the spectral properties of chloro ketone **16**, obtained by the oxidation of **15**. Chloro ketone **16** displays an NMR methyl signal at 1.63 ppm in deuteriochloroform which is shifted downfield by ca. 4 Hz in benzene. This is in accord with the presence of an equatorial methyl group at C-4. Infrared absorption at 5.81 μ and an ultraviolet maximum at 298 nm require an axial C-4 chlorine in ketone **16**.

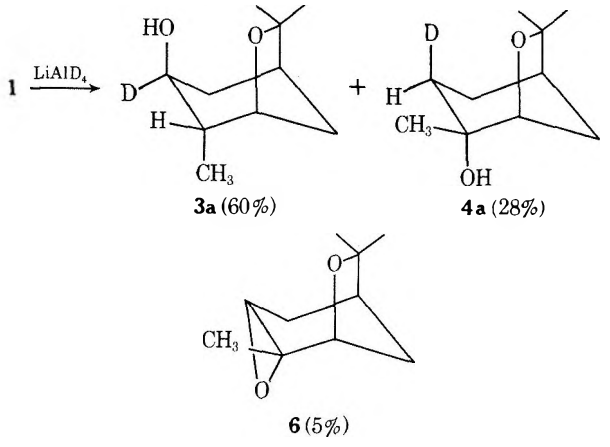
Although cineole chlorohydrin (**1**) undergoes thermal equilibration favoring pinol chlorohydrin (**15**) at temperatures above 100 °C,[8] it is stable in refluxing THF. Cineole chlorohydrin (**1**) is also recovered unchanged when treated with 1 equiv of lithium tri-*tert*-butoxyhydride in refluxing THF, suggesting that the rearrangement of **13** to **17** involves electrophilic catalysis[9] by a specific aluminum species.

It was independently established that pinol chlorohydrin (**15**), although largely recovered unchanged, is in part converted to ketone **12** by treatment with 1 equiv of lithium aluminum hydride and gives alcohol **3** when reacted with excess hydride. Intermediate **17** can now be added to the pathway involved in the conversion of **1** to **3**; in this instance the hydride at C-3 which migrates is anti to the departing chlorine at C-4.

Further verification for this path for the formation of alcohol **3** was provided by the reduction of cineole chlorohydrin (**1**) with lithium aluminum deuteride to produce the products shown in Scheme I, along with a total of 4–5% of three un-



Scheme I



identified substances, none of which appeared to be alcohol **5**.

The position of the deuterium label in alcohol **3a** was easily determined from its NMR spectrum, which showed a signal at 4.03 ppm for the C-5 bridgehead proton as the only downfield resonance. A proton at C-4 was indicated by the methyl doublet at 0.95 ppm.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Infracord. NMR spectra were recorded with a Varian Associates A-60 spectrometer. Mass spectra were measured by the Purdue University Spectral Service using a Hitachi RMU-6A spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

Lithium Aluminum Hydride Reduction of (±)-*endo*-6-Hydroxy-*endo*-7-chlorocineole (1). A mixture of 313 mg (1.53 mmol) of **1** and 76 mg (2.00 mmol) of lithium aluminum hydride in 25 ml of THF was heated at reflux for 56 h. The solution was cooled, water was added, and the salts were removed by filtration and washed with ether. The organic solution was dried ($MgSO_4$) and evaporated to leave 216 mg of an oil. Vpc using a 5 ft, 10% 20M Carbowax column at 110 °C furnished four products. *trans*-4-Hydroxydihydropinol (4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-4α-ol, **4**) (retention time 29 min, 32%) showed IR (CCl_4) 2.87, 3.0, 7.26, 7.31, 8.19, 8.72, 9.18, 9.31, 9.78, and 10.92 μ; NMR ($CDCl_3$) 1.23 [s, 6, $(CH_3)_2C$–], 1.37 (s, 3, CH_3CO), 1.5–2.0 (m, 6), 2.19 (m, 2), and 3.82 ppm (d, 1, J = 5 Hz, –CHO). *endo*-6-Hydroxycineole (**2**) (retention time 36 min, 5.5%) displayed IR (CCl_4) 2.78, 2.89, 7.27, 7.32, 8.30, 8.88, 9.17, 9.41, 9.69, 10.19, and 10.98 μ; NMR ($CDCl_3$) 1.14 and 1.27 [s, 6, $(CH_3)_2C$–], 1.34 (s, 3, CH_3CO), and 3.55 ppm (q, 1, $W_{1/2}$ = 20 Hz, –CHO). *cis*-3-Hydroxy-*trans*-dihydropinol (4α,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3β-ol, **3**) (retention time 46 min, 50%) exhibited IR (CCl_4) 2.81, 2.90, 7.15, 7.27, 7.36, 9.18 and 10.05 μ; NMR ($CDCl_3$) 0.95 (d, 3, J = 8 Hz, CH_3CH–), 1.21 and 1.48 [s, 6, $(CH_3)_2CO$], 1.7–2.2 (m, 2), 2.33 (s, 1, –OH), 3.46 (m, 1, $W_{1/2}$ = 20 Hz, –CHO) and 4.06 ppm (q, 1, $W_{1/2}$ = 14 Hz, –CHOH). *trans*-3-Hydroxy-*cis*-dihydropinol (4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3α-ol, **5**) (retention time 55 min, 11%) showed IR (CCl_4) 2.77, 2.90, 7.26, 7.32, 8.88, 9.05, 9.53, 9.79, 10.11, 10.39, 10.58, 10.71, and 11.17 μ; NMR ($CDCl_3$) 1.09 (distorted d, 3, J = 8 Hz, CH_3CH–), 1.19 and 1.33 [s, 6, $(CH_3)_2CO$], 1.2–2.7 (m, 7), 3.62 (q, 1, $W_{1/2}$ = 26 Hz, –CHO), and 3.80 ppm (d, 1, J = 5 Hz, –CHOC).

***trans*-4-Hydroxydihydropinol (4).** A solution of 224 mg of pinol oxide (**6**) and 100 mg of lithium aluminum hydride in 10 ml of THF was heated at reflux for 8 h. The usual workup gave 226 mg of an oil which by GLC analysis was shown to be a mixture of 74% of alcohol **4** and 26% of pinol oxide (**6**). An analytical sample of **4** was obtained by GLC and showed IR and NMR spectra identical with those of alcohol **4** described above.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.47; H, 10.78.

Reaction of Cineole Chlorohydrin (1) with Sodium Hydride. A solution of 55 mg of **1** and 29 mg of a 57% mineral oil dispersion of sodium hydride was heated at reflux in THF for 25 h. The mixture was cooled, neutralized with dilute hydrochloric acid, and extracted with ether. The ether solution was dried ($MgSO_4$) and carefully evaporated to give 45 mg of pinol oxide (**6**) which was homogeneous according to GLC analysis on a 10% Carbowax column.

***cis*-Dihydropinol (9).** A solution of 825 mg of pinol (**7**) in 40 ml of absolute ethanol was hydrogenated at ambient temperature and

1 atm using platinum oxide as catalyst. The mixture was filtered, diluted with water, and extracted with ether. The ether solution was dried and evaporated to afford 700 mg of colorless liquid which contained 45% of **9** according to GLC analysis. A pure sample of **9** was obtained by GLC and showed IR (CCl_4) 7.27, 7.36, 7.62, 7.71, 7.95, 8.23, 8.65, 8.86, 9.08, 9.22, 9.60, 9.83, 10.05, 10.20, 10.36, 10.57, 10.71, 11.18, and 11.57 μ; NMR ($CDCl_3$) 0.89 (m, 3, CH_3CH–), 1.20 and 1.38 [s, 6, $(CH_3)_2CO$], 1.24–1.95 (m, 7), 2.38 (m, 1), and 3.98 ppm (d, 1, J = 7 Hz, –CHO–).

***trans*-3-Hydroxy-*cis*-dihydropinol (5).** To a solution of 1.49 g (9.8 mmol) of pinol (**7**) in 40 ml of dry THF at 0 °C under nitrogen was added 4.3 ml of 2.3 M borane in THF. The mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was cooled to 0 °C and 5.3 ml of 3 M sodium hydroxide solution was added followed by the dropwise (5 min) addition of 5.3 ml of 30% hydrogen peroxide. The mixture was kept at ambient temperature for 1 h, diluted with water, and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to afford 1.6 g of liquid which was distilled to give pure **5**, bp 71–75 °C (0.18 mm), n^{25}D 1.4805.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.66; H, 10.75.

***cis*-Dihydropinol-3-one (4β,7,7-Trimethyl-6-oxabicyclo-[3.2.1]octan-3-one, 8).** A solution of 170 mg of **5** in 10 ml of acetone was treated with Jones reagent until the orange color persisted. The usual workup gave 132 mg of ketone **8**. An analytical sample was obtained by GLC and showed IR (CCl_4) 5.83, 7.07, 7.26, 7.33, 7.44, 8.44, 8.86, 10.17, and 10.38 μ; NMR ($CDCl_3$) 1.10, 1.21, and 1.24 (s, 9, 3 CH_3C), 1.8–2.9 (m, 6), and 4.27 ppm (d, 1, J = 5.5 Hz, –CHOC).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.45; H, 9.52. Found: C, 71.62; H, 9.75.

***cis*-3-Hydroxy-*cis*-dihydropinol (4β,7,7-Trimethyl-6-oxabicyclo[3.2.1]octan-3β-ol, 10).** A solution of 300 mg (1.78 mmol) of ketone **8** in 15 ml of THF was refluxed with 55 mg (1.45 mmol) of lithium aluminum hydride for 66 h. The mixture was worked up in the usual manner to give 240 mg of an oil which on GLC analysis was shown to be 98% **10** and 2% **5**. An analytical sample of **10** was obtained by GLC and exhibited IR (CCl_4) 2.80, 6.86, 7.13, 7.27, 7.35, 8.08, 8.52, 8.89, 9.46, 9.60, 10.37, and 11.29 μ; NMR ($CDCl_3$) 1.08 (d, 3, J = 7 Hz, CH_3CH–), 1.21 and 1.54 [s, 6, $(CH_3)_2CO$], 1.6–2.8 (m, 7), 3.84 (t, 1, J = 5 Hz, –CHOH), and 4.03 ppm (d, 1, J = 7 Hz, –CHOC).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.81; H, 10.81.

Attempted Equilibration of Ketone 8. A 20-mg sample of ketone **8** in 0.30 ml of methanol containing sodium methoxide (from 5.2 mg of sodium) was kept at ambient temperature for 35 min. The yellow-red solution was neutralized with dilute hydrochloric acid and extracted with ether. The ether solution was dried and evaporated to yield 15 mg of a single product which was obtained pure by GLC: IR (CCl_4) 2.89 and 5.95 μ; NMR ($CDCl_3$) 1.23 [s, 6, $(CH_3)_2CO$], 1.76 (s, 3, CH_3C=C), and 6.75 ppm (m, 1, CH=CCO–). The infrared spectrum of this compound was identical with that of an authentic sample of 8-hydroxycarvotanacetone (**11**).[2,6]

***trans*-Dihydropinol-3-one (4α,7,7-Trimethyl-6-oxabicyclo[3.2.1]octan-3-one, 12).** Approximately 30 mg of alcohol **3** was treated with Jones reagent until the orange color persisted. The usual workup afforded 22 mg of an oil which was homogeneous by GLC. A sample of **12** purified by GLC showed IR (CCl_4) 5.89, 7.14, 7.31, 7.40, 8.36, 8.87, 9.04, and 10.03 μ; NMR ($CDCl_3$) 1.00 (d, 3, J = 7 Hz, CH_3CH–), 1.22 [s, 6, $(CH_3)_2CO$], 1.5–2.6 (m), and 4.20 ppm (m, 1, –CHO); NMR (C_6H_6) 0.69 (d, 3, J = 7 Hz, CH_3CH–), 1.00 and 1.10 [s, 6, $(CH_3)_2CO$], and 3.89 ppm (q, 1, $W_{1/2}$ = 14 Hz, –CHO); mass spectrum m/e (rel intensity) 168 (90), 153 (12), 125 (21), 111 (15), 110 (16), 109 (23), 99 (19), 97 (100), 82 (45), 69 (26), 67 (46), 57 (34), 55 (39), 43 (43), and 41 (39).

Cineole Chlorohydrin (1) and 1 Equiv of Lithium Aluminum Hydride. A mixture of 1.172 g (5.7 mmol) of **1** and 56 mg (1.5 mmol, 5.9 mmol of hydride) in 50 ml of THF was heated at reflux for 72 h. The usual workup gave 1.082 g of light yellow oil. Preparative TLC of 204 mg of this oil gave 100 mg of a 3:2 mixture (NMR analysis) of pinol chlorohydrin (**15**) and cineole chlorohydrin (**1**), and 22 mg of ketone **12**. An analytical sample of pinol chlorohydrin (4α-chloro-4β,7,7-trimethyl-6-oxabicylo[3.2.1]octan-3α-ol, **15**) was obtained by column chromatography on silica gel using pentane–ether as eluent followed by recrystallization from hexane: mp 77–78 °C; IR 2.90, 6.89, 7.23, 7.31, 7.70, 8.15, 8.25, 8.50, 8.92, 9.1–9.5, 9.72, 9.98, 10.42, 10.69, 11.10, 11.35, 12.00, 12.68, and 13.50 μ; NMR ($CDCl_3$) 1.18 and 1.35 [s, 6, $(CH_3)_2CO$], 1.63 (s, 3, CH_3CCl), 1.85–2.35 (m, 5), 3.98 (m, 1, –CHCl), and 4.12 ppm (d, 1, –CHO); molecular ions at m/e 184 and 186.

Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.31. Found: C, 58.39; H, 8.25.

Pinol chlorohydrin (**15**) decomposed to some extent to pinol oxide (**6**) and ketone **12** during GLC using a 15% Carbowax colum at 180 °C. The decomposition could be minimized by using a short column. GLC of the acetate derivatives of alcohols **15** and **1** could be carried out without decomposition. Thus 160 mg of the crude reaction product described above was acetylated with acetic anhydride and pyridine. The volatile reagents were removed in vacuo and the residue was separated on a 10% Carbowax column at 145 °C to give the acetate derivative of **15** (retention time 36 min): IR 5.72, 7.27, 7.31, 8.09, 9.29, and 9.52 μ; NMR ($CDCl_3$) 1.25 and 1.49 [s, 6, $(CH_3)_2CO$], 1.58 (s, 3, CH_3CCl), 2.13 (s, 3, CH_3CO_2–), 1.9–2.6 (m, 4), 4.10 (d, 1, J = 5 Hz, –CHOC), and 5.30 (m, 1, $W_{1/2}$ = 18 Hz, –CHOAc); mass spectrum m/e (rel intensity) 248 (3), 246 (8), 186 (17), 151 (96), 123 (21), 111 (36), 97 (27), and 43 (100). The acetate derivative of alcohol **1** (retention time 44 min) was identified by comparison of spectra with those of an authentic sample.[2]

Pinol Chlorohydrin (15) and Lithium Aluminum Hydride. A. 1 Equiv. A mixture of 273 mg (1.3 mmol) of **15** and 14 mg (0.37 mmol, 1.5 equiv) of lithium aluminum hydride was heated at reflux for 71 h. The mixture was worked up in the usual manner to give 240 mg of a clear oil which partially crystallized on standing. The solid was separated and recrystallized from hexane to give 72 mg of **15**, mp 74–75 °C. The mother liquor and remainder of the oil were purified by TLC and gave 57 mg of **15** and 36 mg of ketone **12**.

B. Excess Lithium Aluminum Hydride. A mixture of 500 mg (2.5 mmol) of **15** and 250 mg (6.6 mmol) of lithium aluminum hydride was heated at reflux in THF for 72 h. The usual workup gave 375 mg of clear oil. Preparative TLC of 275 mg of this oil on silica gel using pentane–acetone as eluent gave a 20:1 mixture of alcohols **3** and **5** (NMR analysis).

***trans*-4-Chlorodihydropinol-3-one (4α-Chloro-4β,7,7-trimethyl-6-oxabicyclo[3.2.1]octan-3-one 16).** To a vigorously stirred solution of 1.6 g (7.8 mmol) of **15** in 25 ml of acetone was slowly added Jones reagent (ca. 2.5 ml) until the color persisted. Isopropyl alcohol (0.25 ml) was added and the salts were removed by filtration and washed thoroughly with ether. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to yield 1.4 g of colorless oil. Column chromatography using silica gel and ether–pentane gave 1 g of colorless liquid: IR 5.80, 6.83, 6.90, 7.08, 7.21, 7.30, 7.42, 7.69, 8.26, 8.42, 8.91, 9.13, 9.39, 9.58, 9.72, 9.90, 11.98, 12.15, and 12.99 μ; λ_{max} (MeOH) 298 nm (ϵ 40); NMR ($CDCl_3$) 1.15 and 1.20 [s, 6, $(CH_3)_2CO$], 1.63 (s, 3, CH_3CCl), 2.0–3.0 (m, 5), and 4.20 ppm (d, 1, –CHO); NMR (C_6H_6) 0.97 [s, 6, $(CH_3)_2CO$], 1.70 (s, 3, CH_3CCl), 1.8–2.2 (m, 5), and 4.02 ppm (d, 1, –CHO); mass spectrum m/e (rel intensity) 204 (13), 202 (39), 167 (15), 123 (18), 116 (15), 109 (22), 97 (100), 95 (10), 90 (12), 89 (11), 83 (16), 82 (10), 81 (50), 79 (17), 69 (29), 67 (11), 59 (12), 55 (25), 53 (28), 43 (72), 41 (64), and 39 (42).

Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.19; H, 7.52; Cl, 17.40.

Reduction of Cineole Chlorohydrin (1) with Lithium Aluminum Deuteride. A mixture of 238 mg (1.39 mmol) of **1** and 100 mg (9.05 mmol) of lithium aluminum deuteride was heated at reflux in 20 ml of THF for 53 h. The usual workup gave 190 mg of clear oil which was separated into the following five components by GLC using a 10% Carbowax column at 110 °C (a) pinol oxide (**6**, retention time 5 min, 5%); (**b**) alcohol **4a** (retention time 15 min, 28%), showed a molecular ion at m/e 171; (c) hydroxycineole **2** (retention time 20 min, ca. 3%), displayed a molecular ion at m/e 171; (d) alcohol **3a** exhibited NMR signals at 0.95 (d, 3, J = 7.5 Hz, CH_3CH–), 1.21 (s, 3, CH_3CO), 1.49 (s, 3 CH_3CO), and 4.07 ppm (q, 1, $W_{1/2}$ = 23 Hz, –CHO); molecular ion at m/e 171; and (e) an alcohol tentatively assigned as *trans*-3-hydroxy-*trans*-dihydropinol (4α,7,7-trimethyl-6-oxabicyclo-[3.2.1]octan-3α-ol) (retention time 58 min, 2%) showed NMR ($CDCl_3$) 0.88 (d, 3, J = 6 Hz, CH_3CH–), 1.18 and 1.40 [s, 6, $(CH_3)_2CO$], and 4.21 ppm (m, 1, $W_{1/2}$ = 26 Hz, –CHO); molecular ion at m/e 171.

Registry No.—**1**, 60760-99-8; **2**, 60761-00-4; **3**, 60761-01-5; **3a**, 60705-66-0; **4**, 60761-02-6; **5**, 60761-03-7; **6**, 38235-59-5; **7**, 60761-04-8; **8**, 60705-67-1; **9**, 60761-05-9; **10**, 60761-06-0; **11**, 7712-46-1; **12**, 60705-68-2; **15**, 60705-69-3; **15** acetate, 60705-70-6; **16**, 60705-71-7; *trans*-3-hydroxy-*trans*-dihydropinol, 60761-07-1; $LiAlH_4$, 16853-85-3; $LiAlD_4$, 14128-54-2.

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Selective Halogen–Lithium Exchange in 2,5-Dibromobenzenes and 2,5-Dibromopyridine[1]

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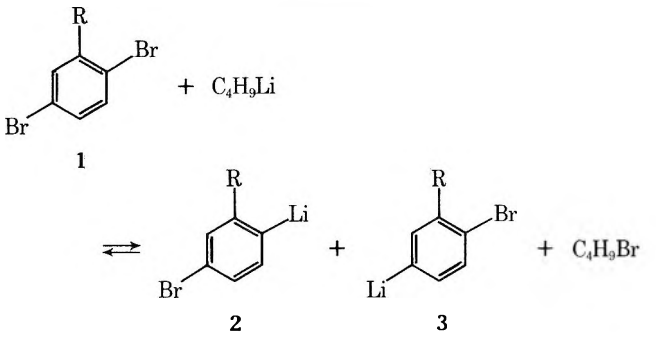
Reaction of a series of 2,5-dibromo-substituted aromatic systems with 1 equiv of *n*-butyllithium at −100 °C results in high selectivity of halogen–metal exchange when the substituent contains unshared electrons. The results suggest that product distribution at −100 °C is determined by thermodynamic rather than kinetic factors. Fair to excellent yields of derivatives of the monolithium intermediates have been obtained. Reaction of 2,5-dibromopyridine with 1 equiv of *n*-BuLi gives exclusively 2-bromo-5-lithiopyridine, which was converted in high yield into 2-bromo-5-deuteriopyridine. Reactions of 2- and 3-lithiopyridine, including their exchange with 2- and 3-bromopyridine, are described.

While selective metalation of substituted aromatic systems with alkyllithium generally occurs ortho to groups containing unshared electrons, an effect attributed to coordination of lithium with the attached functional group,[2] there has been little attention afforded[3] to selective halogen–lithium exchange in substituted dibromobenzenes (Scheme I). Extensive studies by Gilman and his co-workers[4] have established that halogen–metal exchange involves an equilibrium between reactants and products in which the lithium atom resides principally on the more electronegative carbon atom. Thus, one might anticipate that exchange in dibromobenzenes of type **1** would lead to a thermodynamically controlled mixture of **2** and **3**, possibly independent of kinetic factors which might influence the proportion of **2** and **3** formed initially.

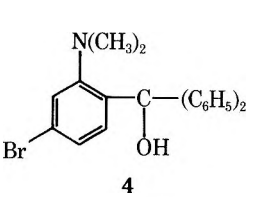
Scheme I



Since we were specifically interested in possible utilization of intermediates of type **2** and/or **3** for synthetic purposes, we have examined exchange in **1** with 1 equiv of *n*-C_4H_9Li in tetrahydrofuran (THF) at very low temperature (−100 °C). The course of reactions was determined by examining aliquots quenched with water, which were subsequently analyzed for starting material and the isomeric monobromobenzenes derived from **2** and **3** by GLC and/or NMR. With the exception of **1e**,[5] exchange was quite rapid and no appreciable change in ratio of products was observed after a few minutes. The results obtained are shown in Table I.

It is apparent that the product distribution shown in Table I does not correlate with Hammett σ functions (electrophilic substitution);[2b] however, with the possible exception of carboxylate,[7] the lithium atom in the product is preferentially located on the most electronegative carbon atom as judged by the inductive effect of the substituent. Whether this result is indeed a function of the inductive effect or a consequence of stabilization of the product by coordination of lithium with the substituent is not known; results with 2,5-dibromopyridine, discussed subsequently, suggest the latter and that the products are those determined by thermodynamic control.

In certain cases the aryllithium derivatives of **1** were elaborated by reaction with electrophiles. Warming the product derived from **1a** effected alkylation by *n*-C_4H_9Br, formed by exchange, to give a 70% yield of 5-bromo-2-*n*-butyltoluene and 2-bromo-5-*n*-butyltoluene in the approximate ratio of 3/7. Decomposition of the product from **1c** with water gave a 70% yield (isolated) of 3-bromo-*N*,*N*-dimethylaniline; reaction of the product from **1c** with benzophenone gave carbinol **4**, isolated pure in 34% yield. Treatment of the aryllithium obtained from **1d** with benzophenone gave 5-bromo-1,1-diphenylphthalide (**5**, pure 42% yield) while reaction of the product



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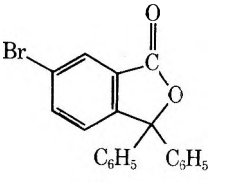

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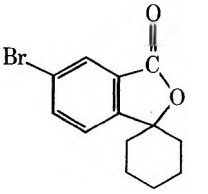

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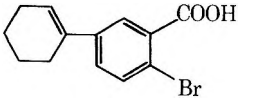


7

from **1d** with cyclohexanone gave lactone **6** and the acid **7**, isolated pure in 45 and 5% yields, respectively. The structure of **7** was assigned by comparison of its NMR spectrum with those of methyl 2-bromobenzoate and methyl 3-bromobenzoate.[8]

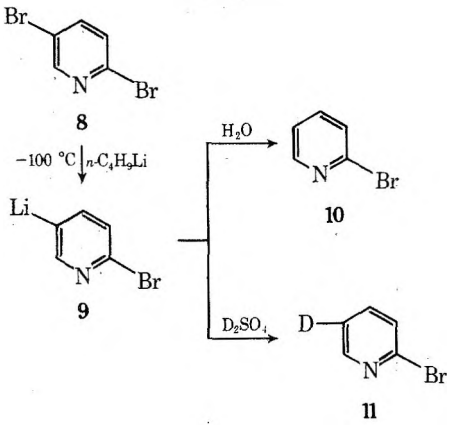
Reaction of 2,5-dibromopyridine (**8**) with 1 equiv of *n*-C_4H_9Li at −100 °C was rapid and complete and gave >99% 2-bromo-5-lithiopyridine (**9**, Scheme II). The product obtained by addition of water was essentially pure 2-bromopyridine (**10**); 3-bromopyridine was detectible (~1%) by GLC. Elaboration of **9** with D_2SO_4 gave a quantitative yield of 2-

Table I. Reactions of 1 with n-C_4H_9Li

Reactant 1	% exchange[a]	Ortho lithiation (ratio)	Meta lithiation (ratio)
1a (R = CH_3)	100	30[b]	70[b]
1b (R = NO_2)	100	100[c]	0[c]
1c [R = $N(CH_3)_2$]	100	95	5
1d (R = CO_2^-)	91[d]	90[d]	~10[d]
1e (R = NH^-)	10[e]	0[e]	100[e]

[a] Based on ratio of monobromobenzenes to 1 in aliquots as determined by GLC. [b] The ratio of monobromobenzenes was determined by NMR. The ratio of *o*-bromotoluene and *m*-bromotoluene did not change when excess dibromotoluene was added to the lithiated product. [c] Considerable by-products formed, thus it is probable that metalation also occurred at the meta position.[6] The only monobromobenzene detected, isolated (50% yield), was pure *m*-bromonitrobenzene. [d] Treatment of crude products with CH_2N_2 and analysis of esters by GLC; NMR of monobromides established nearly exclusive ortho lithiation. [e] Three equivalents of N-C_4H_9Li at −78 °C; products resulting from butylation by derived n-C_4H_9Br were observed and studies at higher temperature were not conducted. At −100 °C and with 3 equiv of n-C_4H_9Li no exchange was observed.

Scheme II

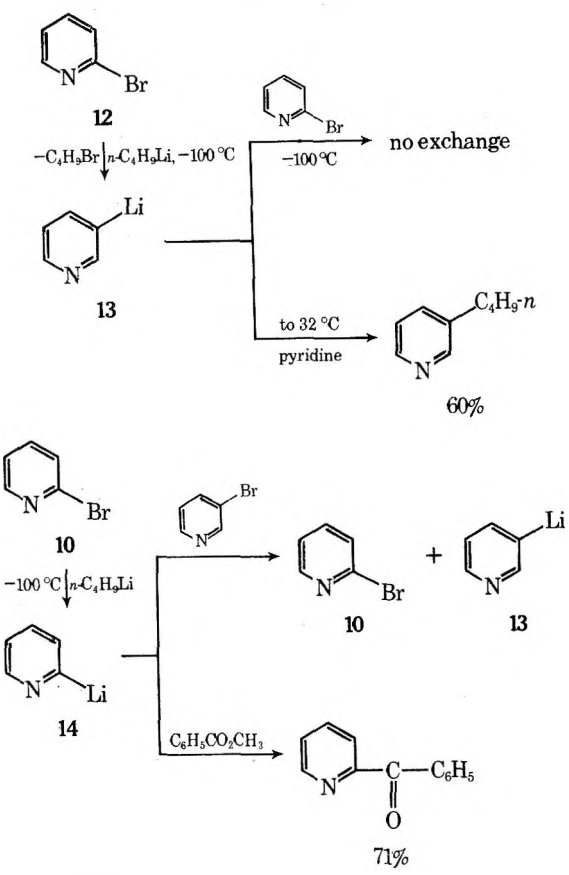


bromopyridine (**11**) which, by mass spectral analysis showed 85% incorporation of deuterium.

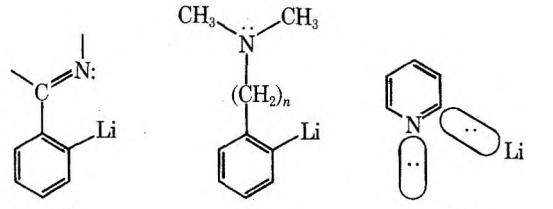
The high selectivity of lithium–halogen exchange at the 5 position of **8** was not expected since the 2 position in pyridine is more electron deficient (more electronegative) than the 5 position. Furthermore, if initial coordination of n-butyllithium with the heteroatom[2] is to play a role in determining initial exchange, then the 2 position would be favored. The above results are, however, consistent with the thermodynamic stability of the corresponding derived lithiopyridines (Scheme III). 3-Lithiopyridine (**13**), formed rapidly and nearly quantitatively at −100 °C from **12**, does not undergo exchange[9] with 2-bromopyridine (−100 °C, 50 min); recovered 2-bromopyridine (70%) contained only a trace of 3-bromopyridine which is thought to be a consequence of incomplete initial exchange from **12**. By contrast, 2-lithiopyridine (**14**), formed rapidly and in high yield at −100 °C from 2-bromopyridine (**10**), undergoes rapid exchange with 3-bromopyridine at −100 °C to give 2-bromopyridine and 3-lithiopyridine. The ratio of 2-bromopyridine and 3-bromopyridine (after water quench) was 79/21 after 20 min at −100 °C. That this ratio was not higher is thought to reflect the fact that 2-lithiopyridine is more reactive than 3-lithiopyridine and is partly consumed at −100 °C by 2-bromopyridine; consequently stoichiometry for complete exchange could not be maintained.

It is interesting to note that heteroatoms as shown in **15**,[2,10] and presumably as in **16**,[2] containing electrons which can be

Scheme III



orthogonal or noncoplanar to the plane containing lithium, can stabilize o-lithio derivatives by coordination while the heteroatom in **17**, in which the unshared electrons are coplanar with lithium, destabilize the aryllithium derivative.



The above results, coupled with those summarized in Table I, suggest that thermodynamic rather than kinetic effects determine the selectivity observed in halogen–metal exchange in dibromo aromatic systems. Such reactions are of synthetic use since selectivity is generally high and fair to good yields of elaborated products are obtained.

Some attempts were made, incidental to this study, to effect condensation of lithiopyridyls **13** and **14** with 2-bromo- and 3-bromopyridine to give bipyridyls; however, such reactions gave tarry mixtures. A convenient synthesis of 3-n-butylpyridine was developed and is shown in Scheme III. Other derivatives of **13** and **14** were prepared and are described in the Experimental Section.

Experimental Section

I. Bromine–Lithium Exchange of2,5-Dibromobenzenes. A. Reaction of 2,5-Dibromotoluene (1a). General Procedure. A solution of n-butyllithium (0.02 mol, 8.65 ml of 2.3 M solution in hexane) was added to a cold (−100 °C, liquid N_2–ether) solution, under N_2, containing 2,5-dibromotoluene (5.88 g, 0.02 mol) and dry (freshly distilled from $LiAlH_4$) THF (125 ml) while maintaining the mixture at −90 to −100 °C.

Aliquots (10 ml) were quenched with 50 ml of water. The resulting mixture was extracted with ether, dried ($MgSO_4$), concentrated, and

analyzed by GLC (6 ft × 0.25 in., 20% SE-30, 150 °C, 60 ml/min He) to determine the ratio of starting material (t_R 3.75 min) to monobromotoluenes (t_R 1.62 min). The residues were then analyzed by NMR to determine the ratio of *m*-bromotoluene (δ 2.11, $ArCH_3$) to *o*-bromotoluene (δ 2.26, $ArCH_3$). The first aliquot, taken after 30 min, showed no unchanged **1a**. The ratio of *o*-bromotoluene to *m*-bromotoluene (~70/30) did not change significantly over a period of 120 min.

B. Reaction of 1-Nitro-2,5-dibromobenzene (1b). Reaction was carried out as in IA. An aliquot (10 ml) was quenched with 10% hydrochloric acid and processed as in IA. Analysis by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 140 °C, 45 ml/min He) showed *m*-bromonitrobenzene (t_R 3.25 min), no *o*-bromonitrobenzene (t_R 4.75 min), and a trace of 2,5-dibromonitrobenzene (t_R 12.00 min). The entire reaction was quenched in 10% HCl and worked up as in IA. The monobromobenzenes were collected by distillation (bp 88–95 °C, 1.0 Torr). No *m*-bromonitrobenzene could be detected by NMR (aromatic, comparison with authentic samples) or by GLC. The residue from distillation was tarry and contained no *m*-bromonitrobenzene or *o*-bromonitrobenzene as indicated by GLC. The isolated yield of pure *m*-bromonitrobenzene was 50%.

C. 2,5-Dibromo-*N,N*-dimethylaniline (1c) [prepared from 2,5-dibromoaniline (0.04 mol), methyl iodide (40 g, 0.28 mol), and NaH (0.10 mol) in THF; 77% yield, bp 90 °C (0.35 Torr); NMR ($CDCl_3$) δ 2.78 (s, 6) 7.2 (m, 3)].

Anal. Calcd for $C_8H_9Br_2N$: C, 34.44; H, 3.25; N, 5.02; Br, 57.29. Found: C, 34.69; H, 3.38; N, 4.86; Br, 57.41.

2-Bromo-*N,N*-dimethylaniline [bp 40 °C (0.25 Torr), lit.[11] bp 107–108 °C (14 Torr); NMR ($CDCl_3$) δ 2.75 (s, 6), 7.00 (m, 4)] and **3-bromo-*N,N*-dimethylaniline** [bp 70 °C (0.45 Torr), lit.[12] bp 100–104 °C (2 Torr); NMR ($CDCl_3$) δ 2.75 (s, 6), 6.8 (m, 4)] were prepared by the procedure of Borsch and Hassid.[13]

Reaction of **1c** was carried out as in IA.

Aliquots were quenched with water, extracted with ether, dried ($MgSO_4$), and concentrated. The first aliquot (1 h) showed by GLC (as in IA, 190 °C) no unchanged **1c** (t_R 9.25 min), 3-bromo-*N,N*-dimethylaniline (95% by peak height, t_R 6.00 min), and 2-bromo-*N,N*-dimethylaniline (<5%, t_R 3.75 min).

D. 2,5-Dibromobenzoic acid (1d) (mp 154–155 °C, lit.[14] 153 °C, from **1a**, $KMnO_4$, and water in *tert*-butyl alcohol, 73% yield) was treated with 2 equiv of *n*-C_4H_9Li as in IA. **Methyl 2,5-dibromobenzoate** (mp 43–45 °C, lit. 40–41 °C[15]), **methyl 2-bromobenzoate,** and **methyl 3-bromobenzoate** were prepared from the corresponding acids with diazomethane[15] and showed retention times of 2.62, 1.5, and 1.5 min, respectively (5 ft × 0.25 in., 3% SE-30, 190 °C, 30 ml/min He].

Aliquots (10 ml) were quenched with water and the aqueous solution was extracted with ether. The aqueous solution was acidified (concentrated HCl), extracted with ether, dried ($MgSO_4$), and concentrated. The crude residual acids were treated with excess ethereal CH_2N_2; acetic acid was employed to destroy excess CH_2N_2. The ether solution was extracted with aqueous bicarbonate, dried ($MgSO_4$), and concentrated. Analysis (GLC, see above, ID) showed 91% methyl monobromobenzoates (t_R 1.5 min) and 9% methyl 2,5-dibromobenzoate (t_R 2.62 min) (after 100 min). Analysis (NMR) of the methyl monobromobenzoates (collected by GLC) showed it to be nearly pure (>90%) *m*-bromobenzoate.

E. Reaction of 2,5-dibromoaniline (1e) was carried out as IA except that 2 equiv of *n*-C_4H_9Li was employed.

Aliquots were quenched with water, extracted with ether, dried ($MgSO_4$), and concentrated. Analysis was made by GLC (as in IA, 180 °C, 30 ml/min He). Retention times of authentic 2,5-dibromoaniline, *o*-bromoaniline, and *m*-bromoaniline were 11.37, 3.75, and 4.75 min, respectively. Essentially no exchange occurred at −100 °C. The ratio of **1e** to *o*-bromoaniline was 95/5 after 45 min at −78 °C and 90/10 after 135 min; no *m*-bromoaniline (exchange at ortho position) was detected. NMR analysis showed some butylation at −78 °C and considerable butylation when exchange was conducted at higher temperature.

Essentially identical results were obtained when 3 equiv of *n*-C_4H_9Li was employed.

II. Elaboration of 1. A. 2-Bromo-5-butyltoluene and 5-Bromo-2-*n*-butyltoluene. The mixture described in IA was allowed to warm to 32 °C and maintained at this temprature for 48 h. The mixture was processed essentially as described in IA to give a mixture of 2-bromo-5-*n*-butyltoluene and 5-bromo-2-*n*-butyltoluene [70% yield, bp 78–82 °C (1.0 Torr)].

Anal. Calcd for $C_{11}H_{15}Br$: C, 58.16; H, 6.65; Br, 35.18. Found: C, 58.32; H, 6.77; Br, 34.96.

The intensity of NMR signals at δ 2.28 and 2.13 showed that the ratio of the 2-bromo to the 5-bromo isomer was ~3/7.

B. 3-Bromo-*N,N*-dimethylaniline [70% yield from **1c**, see section IB for procedure, bp 75 °C (0.6 Torr), lit.[5b] bp 259 °C (760 Torr), pure by GLC (section IB)].

C. 4-Bromo-2-(*N,N*-dimethylamino)phenyldiphenylcarbinol (4). Reaction of **1c** (0.02 mol) was carried out as in IC; the reaction mixture was stirred for 30 min at −100 ° and benzophenone (0.0203 mol) in dry THF (30 ml) was added. The mixture was allowed to warm to 32 °C, THF was removed (rotary evaporation), and ether (100 ml) and cold 10% sulfuric acid (100 ml) were added. The ether extract was dried ($MgSO_4$) and concentrated to give 6.12 g of product which was recrystallized from petroleum ether (bp 30–60 °C) to give pure **4** [2.60 g, 34% yield, mp 113–114 °C; NMR ($CDCl_3$) δ 2.41 (6 H), 7.4 (18 H), 9.5 (1 H)].

Anal. Calcd for $C_{21}H_{20}BrNO$: C, 65.97; H, 5.27; Br, 20.90; N, 3.66. Found: C, 65.76; H, 5.41; Br, 21.18; N, 3.45.

D. 5-Bromo-1,1-diphenylphthalide (5). Reaction of 2,5-dibromobenzoic acid with *n*-C_4H_9Li was carried out as in section ID and the mixture was treated with benzophenone as described in section IIC. The mixture obtained subsequent to removal of THF was added to ether (100 ml) and water (100 ml). The aqueous layer was separated, made acidic with concentrated HCl, and warmed for 45 min on a steam cone to effect cyclization of the intermediate hydroxy acid to **5**. The acid solution was extracted with ether which was extracted with aqueous bicarbonate to remove acids. The ether extract was dried and concentrated to give 3.33 g of yellow oil which was recrystallized from ethanol to give 1.60 g (32% yield) of pure **5**, mp 118–120 °C.

Anal. Calcd for $C_{20}H_{13}BrO_2$: C, 65.77; H, 3.59; Br, 21.88. Found: C, 65.72; H, 3.52; Br, 21.96.

Chromatography (TLC, silica gel) of the mother liquor gave an additional 12% yield of pure **5**.

E. Spiro[5-bromoisobenzofuran-1(3*H*)-cyclohexan]-3-one (6) and 2-Bromo-5-(1-cyclohexenyl)benzoic acid (7). Reaction of **1d** (0.014 mol) with 2 equiv of *n*-C_4H_9Li was carried out as in ID. The mixture was maintained at −100 °C for 45 min and cyclohexanone (0.0408 mol) in dry hexane (25 ml) was added. The mixture was processed essentially as described in section IID. The ether layer, obtained subsequent to treatment with hot aqueous acid, contained 1.81 g of product (mp 120–130 °C) which gave 1.73 g (45% yield) of pure **6** (mp 132–135 °C, from petroleum ether, bp 63–75 °C).

Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.62; H, 4.71; Br, 28.17.

Acidification of the bicarbonate solution gave 0.5 g of acid, mp 125–148 °C. Recrystallization of this product from acetone–water gave **7** [5% yield, mp 170–171 °C; NMR (Me_2SO-d_6) δ 1.6–2.5 (m, 8), 6.2 (s, 1), 7.4–7.8 (m, 4)].

Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.70; H, 4.73; Br, 28.15.

III. Lithium–Halogen Exchange in Bromopyridines. A. Reaction of 2,5-dibromopyridine (**8**, 0.01 mol) in THF (125 ml) with *n*-C_4H_9Li (0.011 mo) was carried out at −100 °C as described in IA.

Aliquots (10 ml, 20 and 55 min) were quenched in 50 ml of 10% HCl and the solution was extracted with ether. The acid solution was made strongly alkaline with 50% KOH and extracted with ether. The dried ($MgSO_4$) ether extract was concentrated to give residues analyzed by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 120 °C, 30 ml/min He) which showed 2-bromopyridine (t_R 11.37 min, 99%) and less than 1% 3-bromopyridine (t_R 5.00 min). No 2,5-dibromopyridine (t_R 2.37 min at 200 °C) could be detected.

2-Bromo-5-deuteriopyridine. The cold solution, prepared from **8** (0.01 mol) and *n*-C_4H_9Li as described in IIIA, was aged for 30 min at −100 °C and then treated with 2 ml of D_2SO_4. The solution was allowed to warm to 32 °C, poured into dilute H_2SO_4 (200 ml), and extracted with ether. The acid solution was processed as in IIIA to give 1.93 g of crude amine which was analyzed by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 150 °C, 30 ml/min He). Retention times of authentic samples follow: 3-bromopyridine, 1.00 min; 2-bromopyridine, 3.37 min; 3-bromopyridine (absent in the mixture) was used as internal added standard (same response as the 2 isomer). The product was essentially pure 2-bromopyridine (101% yield). Pure 2-bromopyridine was collected by GLC. Mass spectral analysis showed 85% incorporation of deuterium (by comparison of P and P − 1 peaks with undeuterated 2-bromopyridine).[16]

B. Reactions of 3-Bromopyridine (12). 1. 3-Lithiopyridine (**13**) was prepared from **12** (0.02 mol) and *n*-C_4H_9Li (0.02 mol) as described in section IA.

Aliquots (10 ml) were added to 10% HCl (100 ml) and THF was removed (rotary evaporator). The aqueous solution was extracted with ether and made strongly alkaline with 50% KOH. The solution was

extracted with ether, the dried extract was treated with ethereal HCl (100 ml), and ether was removed. The residue was treated with 15% aqueous NaOH and extracted with ether. The dried extract was concentrated and analyzed by GLC (20% Carbowax 20M, 150 °C, 30 ml/min He). Pyridine (98%, t_R 1.5 min) and 3-bromopyridine (2%, t_R 4.87 min) were detected.

2. 3-*n*-Butylpyridine. Pyridine (0.02 mol) was added at −100 °C to a solution of 3-lithiopyridine (0.02 mol), prepared as described above. The solution was allowed to warm to 32 °C, then processed essentially as described in the IIIB1 aliquot. Analysis (GLC, as shown above) showed 3-*n*-butylpyridine (t_R 2.25 min) and pyridine (t_R 1.5 min). Distillation of the crude product gave 1.62 g (60%) of pure 3-*n*-butylpyridine [bp 46–48 °C (1.5 Torr), lit.[17] bp 82–83 °C (10 Torr); NMR ($CDCl_3$) δ 0.9 (t, 3), 1.1–1.7 (m, 4), 2.5 (t, 2), 7.1–7.4 (m, 2), 8.4 (m, 2)].

3. 3-Pyridyldiphenylcarbinol. 3-Lithiopyridine (**13**, 0.022 mol) was treated at −100 °C with benzophenone (0.022 mol). The mixture was allowed to warm to 32 °C and THF was removed (rotary evaporator). Dilute H_2SO_4 (10 ml of 10%) was added and unreacted benzophenone (0.009 mol) was removed by filtration. The acid solution was made basic (KOH) and extracted with chloroform. The product (3.44 g) obtained from the dried chloroform was recrystallized from petroleum ether (bp 30–60 °C) to give 2.82 g (54% yield) of 3-pyridyldiphenylcarbinol (mp 111–114 °C, lit. 115 °C[18]).

4. Reaction of 3-Lithiopyridine (13) with 2-Bromopyridine at −100 °C. A mixture of **13** (0.02 mol), prepared as described above, and 2-bromopyridine (0.02 mol) was stirred at −100 °C for 40 min. The entire mixture was added to 10% HCl (200 ml) and processed essentially as described in IIIA aliquot. Analysis (GLC as in IIIA, 140 °C) showed the ratio of 2-bromopyridine (t_R 9.75 min) to 3-bromopyridine (t_R 6.00 min) to be 96/4. The yield of recovered 2-bromopyridine, determined by adding *o*-bromoanisole (t_R 10.75 min) and making corrections for the relative response factors of each, was 73%.

When the mixture of **13** and **10** was allowed to warm to 32 °C a black tar was obtained which was not processed.

C. Reactions of 2-Bromopyridine (10). 1. 2-Lithiopyridine (14) was prepared and analyzed as described for **13** in section IIIB. Analysis of aliquots (20 min, GLC, 130 °C) showed pyridine (t_R 2.12 min) and no unchanged 2-bromopyridine (t_R 5.62 min).

2. 2-Benzoylpyridine. A solution of **14** (0.0344 mol) was treated after 20 min with methyl benzoate (0.04 mol); the mixture was allowed to warm to room temperature, THF was removed (rotary evaporator), and the residue was partitioned between ether and water. The ether layer was distilled to give 4.46 g (71% yield) of 2-benzoylpyridine [bp 125–135 °C (0.3 Torr); picrate mp 129–130 °C, lit.[19] 124–127 °C].

3. Reaction of 2-lithiopyridine with 3-bromopyridine at −100 °C was carried out as in section IIIB4 (GLC, 6 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W 30/60, 30 ml/min He). Aliquots taken at 20 and 60 min gave identical ratios of 2-bromopyridine (t_R 8.12 min) to 3-bromopyridine (t_R 4.37 min) of 79/21. Some condensation occurred as evidenced by the dark color of the crude product.

Registry No.—**1a**, 615-59-8; **1b**, 3460-18-2; **1c**, 60573-63-9; **1d**, 610-71-9; **1e**, 3638-73-1; **4**, 60573-64-0; **5**, 60573-65-1; **6**, 60573-66-2; **7**, 60573-67-3; **8**, 624-28-2; **10**, 109-04-6; **12**, 626-55-1; **13**, 60573-68-4; **14**, 17624-36-1; *n*-butyllithium, 109-72-8; 2-bromo-5-butyltoluene, 60573-69-5; 5-bromo-2-butyltoluene, 60573-70-8; benzophenone, 119-61-9; cyclohexanone, 108-94-1; 2-bromo-*N*,*N*-dimethylaniline, 698-00-0; 3-bromo-*N*,*N*-dimethylaniline, 16518-62-0; pyridine, 110-86-1; 3-*n*-butylpyridine, 539-32-2; methyl benzoate, 93-58-3; 2-benzoylpyridine, 91-02-1.

References and Notes

(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD 128.
(2) (a) H. Gilman, *Org. React.*, **8**, 261 (1954); (b) *ibid.*, **8**, 262 (1954); (c) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963); (d) W. H. Puterbaugh and C. R. Hauser, *ibid.*, **29**, 853 (1964); (e) D. W. Slocum and F. E. Stonemark, *ibid.*, **38**, 1677 (1973).
(3) The ratio of ortho–meta exchange was reported to be 22:36 by reaction of 2,5-dibromotoluene with *n*-butyllithium in ether at 32 °C: H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940).
(4) (a) S. V. Sunthankar and H. Gilman, *J. Org. Chem.*, **16**, 8 (1951); (b) H. Gilman and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 1843 (1940); (c) H. Gilman and R. G. Jones, *ibid.*, **63**, 1441 (1941); (d) R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1952).
(5) Anions of atoms attached directly to the aromatic ring are known to inhibit halogen–metal exchange: (a) for CH^- cf. W. E. Parham and L. D. Jones, *J. Org. Chem.*, **41**, 1187 (1976); (b) for phenoxides, halogen exchange is generally conducted at 32 °C, cf. H. Gilman, C. E. Arntzen, and F. E. Webb, *J. Org. Chem.*, **10**, 374 (1945); (c) *p*-bromoaniline undergoes exchange at reflux in ether, cf. H. Gilman and G. C. Gainer, *J. Am. Chem. Soc.*, **69**, 1946 (1947).
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(7) Carboxylate is generally considered to have a +I effect (cf. E. S. Gould, "Mechanism and Structure in Organic Chemistry", D. C. Heath, Boston, Mass., 1959, p 207); however, δ_1 is reported to be 0.05 as determined by NMR (cf. Kosower, "Physical Organic Chemistry", Wiley, New York, N.Y., 1968, p 49). The inductive effect of lithium carboxylate in THF is not known.
(8) The aromatic proton (δ 8.2) ortho to both bromine and carbonyl in methyl *m*-bromobenzoate is deshielded to a greater extent than those adjacent to only bromine or carbonyl. There is no absorption at δ 8.2 in methyl *o*-bromobenzoate.
(9) A slow reaction occurs at −100 °C, expectedly more rapid at higher temperatures to give tarry condensation products.
(10) Cf. A. I. Meyers and E. D. Mikelich, *J. Org. Chem.*, **40**, 3158 (1975).
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Reactions of Lithio Derivatives of Carboxylic Acids. 1. 3-Methyl-2-butenoic Acids[1]

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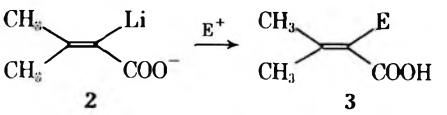
Halogen–metal exchange with 2-bromo-3-methyl-2-butenoic acid at −100 °C leads to a stable lithiovinyl intermediate which reacts with a variety of electrophiles to afford 2-alkylated derivatives in good yields. Reaction of 3-methyl-2-butenoic acid with *n*- and *tert*-butyllithium followed by protonation or alkylation is discussed.

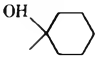
Since 2-bromo-2-alkenoic acids are readily available from 2-alkenoic acids,[3] then possible reaction as shown in Scheme I (**1** → **2** → **3**) appeared attractive as a general method for synthesis of 2-substituted 2-alkenoic acids. The previous observation that salts of bromobenzoic acids[4a] and bromoarylalkanoic acids[4b] form stable lithium intermediates by halogen–metal exchange provided a firm precedent for this sequence; however, it remained to be established[3,5] whether proton removal from allylic (γ) positions (i.e., **1** → **6**) or lithium interchange (i.e., **2** ⇄ **4**) would impose a synthetically unacceptable limitation on such a sequence.

2-Bromo-3-methyl-2-butenoic acid (**1**)[3] was chosen as a model and halogen–metal exchange was conducted in tetrahydrofuran at −100 °C with *n*-butyllithium. The progress of

Table I. Reaction of Lithio Derivative 2 with Electrophiles (E^+)

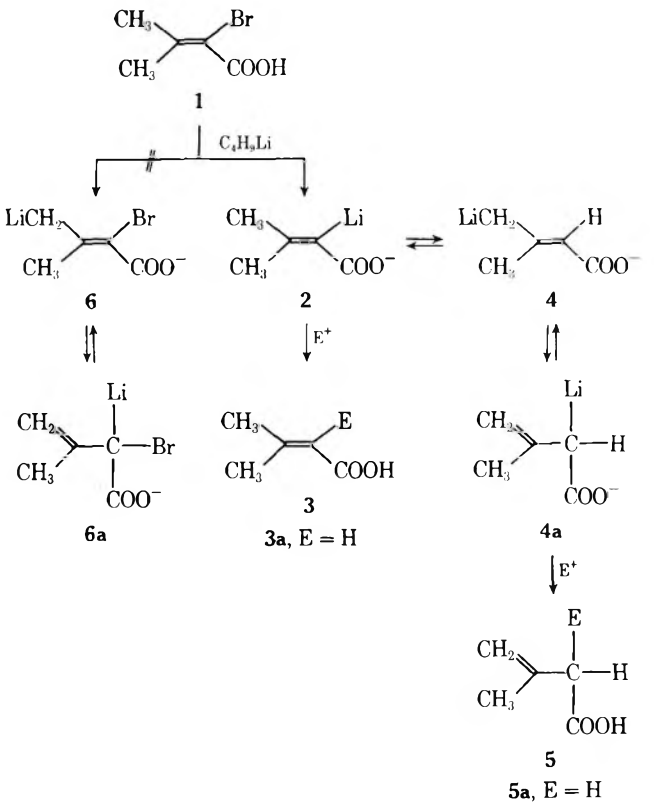


2 3

Electrophile	Product(s)	E	Isolated yield, %	Mp, °C	Ir (acid $\nu_{C=O}$), cm^{-1}
H_2O	3a, 5a	H	98[a]	45–55[b]	1695[c,d]
CH_3OD[e]	3b	D[f]	94[g]	64–66	1695[h]
CH_3CH_2I	3c	CH_2CH_3	79	42.5–44[i]	1686[c]
	3d		30	156.5–157.5 dec	1701[j]
$C_6H_5COC_6H_5$	3e	$C(OH)(C_6H_5)_2$	64	143–144 dec	1692[j]
C_6H_5NCO	3f	$CONHC_6H_5$	58	181.5–182.5 dec	1686[j]
CH_3SSCH_3	3g	SCH_3	59	80–81	1689[h]
$C_6H_5SSC_6H_5$	3h	SC_6H_5	61	85–86	1684[h]

[a] See note 5. [b] Lit.[6] mp of 3a is 69.5–70° C. [c] Melt. [d] Agrees with ref[7] value for 3a. [e] 99% D. [f] Ca. 95% D by NMR. Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 59.18; H, 7.99. [g] See note 8. [h] CCl_4 solution. [i] See Experimental Section. [j] KBr pellet.

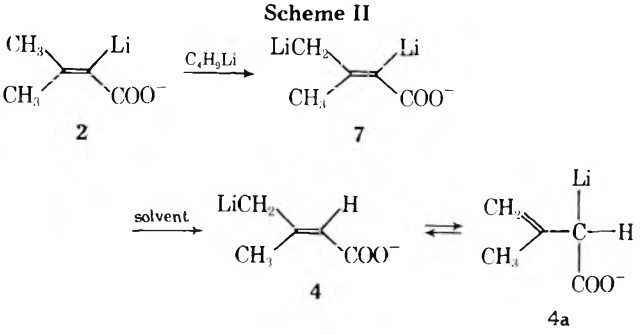
Scheme I



reaction was followed by examining aliquots which were quenched with water (identical results were obtained with saturated aqueous NH_4Cl or 10% aqueous HCl) and analyzed (by NMR) for unchanged 1 and reduced acids **3a** and/or **5a**. Halogen–metal exchange was rapid and complete when the first aliquot was taken 15 min after addition of 2 molar equiv of *n*-butyllithium per mole of acid (at −100 °C). When less than 2 molar equiv of *n*-butyllithium was employed (i.e., 1.8), the product acids (isolated in 98% yield) were 3-methyl-2-butenoic acid (**3a**) and unchanged 1 (ratio **3a**/1 = 75/25). When a 10% excess (i.e., 2.2 equiv) of *n*-butyllithium was employed, the product (isolated in 98% yield) contained mostly **3a** but was contaminated with about 10% **5a**. We were unable to eliminate either small quantities of 1 or **5a** and therefore conducted subsequent experiments with 2.0 equiv of *n*-butyllithium (ratio **3a**/**5a** = 95/5). We found no evidence (other than unchanged 1) for the formation of **6** or **6a**. The lithio derivative **2** reacted with various electrophiles (E^+) to give fair to good yields of 2-substituted 3-methyl 2-butenoic acids (3). The results are summarized in Table I.

The exact process by which **5** is formed remains obscure since there are a number of logical routes for its formation.[3] The fact that the ratio **3a**/**5a** does not change significantly when a solution of the lithio derivative 2 is aged at −100 or −70 °C (6 h) shows that **4** is not formed by direct conversion of **2** to **4**, or, alternatively, if there is an equilibrium between **2** and **4** it is reached rapidly and greatly favors **2**. The absence of isomer **5a**, unless a slight excess of *n*-butyllithium is employed, implicates the trianion **7** (Scheme II) as an intermediate.

Scheme II



Rapid decay of the trianion, precedented by observation with *o*- and *p*-bromophenylacetic acids,[4b] defines one reasonable path for the formation of **5a**. It is not implied that metalation occurs preferentially at either the cis or trans methyl group; however, only trans-alkylated product (**9**, Scheme III) was isolated.

A study of the reaction of 1 with *tert*-butyllithium was made in an attempt to obviate formation of *n*-butyl bromide formed during halogen–metal exchange with *n*-butyllithium. This would be advantageous since it would permit alkylation of **2** with less reactive electrophiles than were employed above. Reaction of 1 with 3 molar equiv of *tert*-butyllithium, however, led to appreciable isomerization to **5a** (ratio **3a**/**5a** = 68/32) after 15 min at −100 °C. These results are not surprising in retrospect since *tert*-butyllithium is a stronger base and possibly more prone to lead to trilithio derivatives. Alternatively, **2** could compete with *tert*-butyllithium in dehydrohalogenation of the *tert*-butyl bromide formed, thereby leading to **3a** and, subsequently, to **5a**.

Katzenellenbogen[10] prepared the lithio derivative **4** (**4a**)

Table II. Lithiation of 3-Methyl-2-butenoic Acid at −100 °C

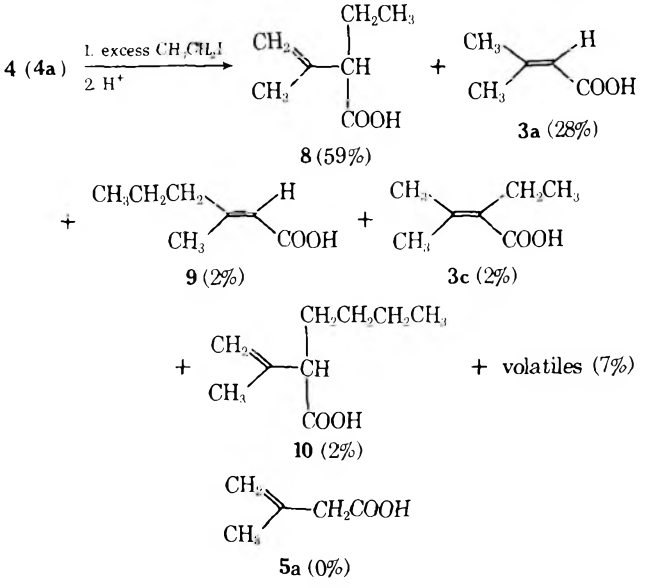
Reaction time, h	Equiv C_4H_9Li	% 5a in product[a]	
		n-C_4H_9Li	t-C_4H_9Li
0.25	2.0	51	65
1.0	2.0	53	75
2.0	2.0	59	75
2.25	3.0[b]	63	75
3.0	3.0	71	79
4.0	3.0	73	80

[a] After quenching in water; remainder was 3a. [b] After adding an additional 1 equiv of butyllithium in the same experiment.

by reaction of 3a with lithium diisopropylamide (LDA) and showed that it undergoes alkylation to give almost exclusively derivatives of 5. While one would expect 4 (4a) to protonate in a fashion analogous to alkylation, neither this result nor the direct formation of 4 (4a) by use of alkyllithium has been reported. The results shown in Table II show that after 1 h the product ratio is not highly time dependent and is not influenced significantly by additional alkyllithium. While these results suggest that 4 (4a) is protonated to 3a/5a up to the ratio 20/80, results described below for alkylation of the reaction mixture do not support such a conclusion.

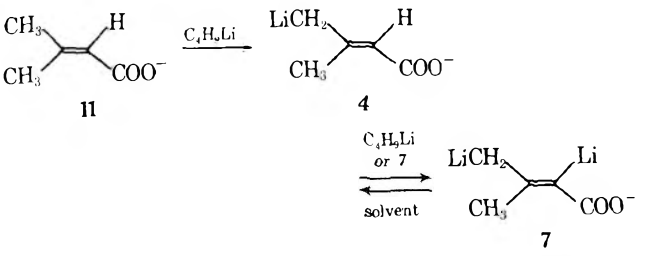
Alkylation of the lithio derivative mixture with excess ethyl iodide added 15 min after addition of 2.0 equiv of n-butyllithium (at −100 °C, see Experimental Section) afforded a mixture of acids which was analyzed by GLC[11] and NMR. The results are shown in Scheme III.

Scheme III



Compounds 3a, 3c, 8, 9, and 10 were isolated (GLC) and characterized by NMR and combustion analysis. Formation of alkylated products 8 and 10 (evidently some n-butyl iodide was formed under the reaction conditions) corroborates Katzenellenbogen's results; only 2% of γ-alkylated product 9 was obtained. The fact that no 5a was formed (NMR analysis of the GLC fraction containing 3a) confirms that alkylation of 4 (4a) was complete. Therefore it is unreasonable to conclude that the high recovery of 3a was a consequence of incomplete alkylation of 4 (4a) and it is strongly suggested that the unmetalated carboxylate salt of 3a (i.e., 11, Scheme IV) was present in the reaction mixture and, analogously, in the reaction products from the protonation experiments. Incomplete metalation of 11 suggests that metalation of 4 (4a) to 7 is competitive with initial metalation of 11 (Scheme IV).

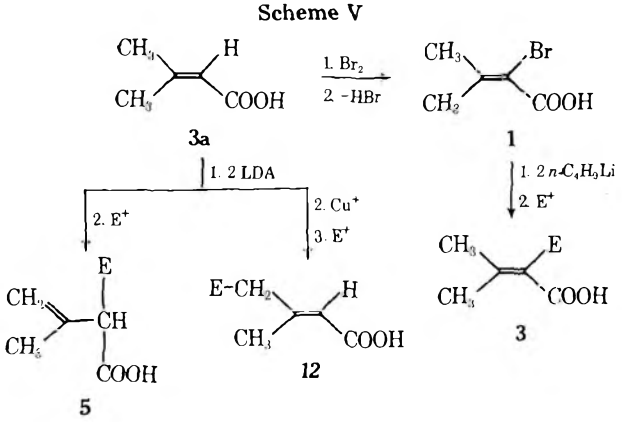
Scheme IV



Failure to isolate dialkylated products is consistent with rapid anion decay of the trianion 7 to 4 (4a). Such decay of trianions is precedented.[4b]

In summary, halogen–metal exchange in acids of type 1 affords reasonable yields of derived acids of type 3. This work complements that of Katzenellenbogen and co-workers;[10] consequently it is now possible (Scheme V) to alkylate acids

Scheme V



of type 3a either at the 2 position, as described herein to give acids of type 3, at the 4 position through the copper dienolate[10] to give acids of type 12, or at the 2 position to give isomerized acids of type 5.

Experimental Section

All reactions involving organolithium reagents were conducted under an atmosphere of nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride or n-butyllithium[12] prior to use. Reaction temperatures of −100 °C were achieved with a diethyl ether–liquid nitrogen bath. All organic residues were dried with anhydrous magnesium sulfate. NMR data were obtained from a JEOL Model JNM-MH-100 100-MHz spectrometer using 1–2% tetramethylsilane as an internal standard; IR data were obtained from a Perkin-Elmer Model 137 spectrometer; GLC analyses were performed with a Varian Model 910 gas chromatograph (thermal conductivity detector). Microanalyses were performed by MHW Laboratories, Garden City, Mich. All melting points were determined on a Mel-Temp heating block apparatus and are corrected.

General Procedure for Halogen–Metal Exchange. 2-Bromo-3-methyl-2-butenoic acid[3] (1, 4.48 g, 0.025 mol, mp 88–90 °C, lit.[3] mp 91.5 °C) and tetrahydrofuran (200 ml) were introduced, under nitrogen, into a 250-ml three-neck flask equipped with a low-temperature thermometer, pressure-equalizing addition funnel, nitrogen inlet, and mechanical stirrer. The reaction mixture was cooled to −100 °C and n-butyllithium (20 ml, 0.050 mol, 2.5 M solution in hexane) was added at a rate such that the temperature did not exceed −90 °C. Fifteen minutes after the addition of n-butyllithium was complete (examination of aliquots showed that formation of 2 was complete at this time), a solution of the electrophile in tetrahydrofuran (25 ml) was added at a rate such that the temperature did not exceed −90 °C. After an additional 15 min at about −90 °C, the reaction mixture was allowed to warm to room temperature (3 h) and poured into water (50 ml). Solvents were removed (rotary evaporation) and the mixture was extracted with two 30-ml portions of ether (to remove neutral material). The aqueous solution was cooled (0 °C) and made acidic (concentrated hydrochloric acid), and the crude product was isolated (solids by filtration; oils by extraction with five 30-ml portions of ether). The crude products were purified by either recrystallization or preparative GLC.[11]

A. 2-Ethyl-3-methyl-2-butenoic acid (3c) was obtained from **2** and ethyl iodide (19.5 g, 0.125 mol). Concentration of the acid-containing organic extracts afforded 2.60 g of colorless, semicrystalline material (mp 25–40 °C). Spectral analysis (NMR) of this material showed it to be a mixture of **3c** (97%, 79% yield) and 2-ethyl-3-methyl-3-butenoic acid (**8**, 3%, 2% yield). This material was purified by preparative GLC to afford pure **3c** as white needles [mp 42.5–44 °C, lit.[13] mp 49.5 °C; NMR ($CDCl_3$) δ 1.02 (t, 3, CH_2CH_3), 1.84 (s, 3, CH_3), 2.08 (s, 3, CH_3), 2.34 (quartet, 2, CH_2CH_3), 12.0 (s, 1, OH)]. Attempts to purify the mixture of crude acids by either recrystallization or sublimation were of limited success.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.60; H, 9.23.

B. 2-(1-Hydroxycyclohexyl)-3-methyl-2-butenoic acid (3d) was obtained from **2** and cyclohexanone (2.45 g, 0.025 mol). The precipitate (3.83 g, mp 106–113 °C dec) obtained upon acidification of the alkaline solution was recrystallized from chloroform to afford 1.48 g (30% yield) of nearly pure **3d** as white needles, mp 135–137.5 °C dec. Two further recrystallizations afforded an analytically pure sample: mp 156.5–157.5 °C dec; NMR (acetone-d_6) δ 1.70 (s, 3, CH_3), 1.98 (s, 3, CH_3), 1.0–2.2 (m, 10, ring CH_2's), 4.2 (broad s, 2, OH's).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.69; H, 9.13.

C. 2-(Hydroxydiphenylmethyl)-3-methyl-2-butenoic acid (3e) was obtained from **2** and benzophenone (9.11 g, 0.050 mol). The precipitated crude product (6.03 g) was recrystallized from a 1:1 mixture of methylene chloride and hexane to afford 4.52 g (64% yield) of nearly pure **3e** [in two crops, mp 131–134 °C dec (sealed tube) and 121–126 °C dec (sealed tube)]. A second recrystallization afforded an analytically pure sample as finely divided white crystals: mp 143–144 °C dec (sealed tube); NMR (acetone-d_6) δ 1.46 (s, 3, CH_3), 1.88 (s, 3, CH_3), 5.30 (broad s, 2, OH's), 7.1–7.8 (m, 10, ArH).

Anal. Calcd for $C_{18}H_{18}O_3$: 76.57; H, 6.42. Found: C, 76.59; H, 6.44.

D. 2-(*N*-Phenylcarbamoyl)-3-methyl-2-butenoic acid (3f) was obtained from **2** and phenyl isocyanate (3.28 g, 0.0275 mol). The precipitated crude product (3.94 g) was recrystallized from water to afford 3.15 g (58% yield) of nearly pure **3f**, mp 174.5–176.5 °C dec (sealed tube). A second recrystallization afforded an analytically pure sample as yellowish needles: mp 181.5–182.5 °C dec (sealed tube); NMR (CF_3CO_2H) δ 2.22 (s, 3, CH_3), 2.40 (s, 3, CH_3), 7.42 (m, 5, ArH), 9.1 (broad s, 1, NH).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.76; H, 5.94; N, 6.26.

E. 2-Methylthio-3-methyl-2-butenoic acid (3g) was obtained from **2** and dimethyl disulfide (2.60 g, 0.0275 mol). Concentration of the acid-containing organic extracts afforded 3.45 g of crude product (mp 52–70 °C); this was recrystallized from hexane to afford 2.04 g (59% yield) of analytically pure **3g** [mp 80–81 °C; NMR ($CDCl_3$) δ 2.12 (s, 3, CH_3), 2.14 (s, 3, CH_3), 2.26 (s, 3, CH_3), 12.0 (s, 1, OH)] as finely divided white crystals.

Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.14; H, 6.84; S, 21.76.

F. 2-Phenylthio-3-methyl-2-butenoic acid (3h) was obtained from **2** and diphenyl disulfide (6.00 g, 0.0275 mol). Concentration of the acid-containing organic extracts afforded 4.46 g of crude product (mp 58–71 °C); this was recrystallized from hexane to afford 2.73 g (61% yield) of analytically pure **3h** [mp 85–86 °C; NMR ($CDCl_3$) δ 2.16 (s, 3, CH_3), 2.20 (s, 3, CH_3), 7.16 (s, 5, ArH), 12.0 (s, 1, OH)] as finely divided white crystals.

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.39. Found: C, 63.60; H, 5.71; S, 15.12.

Reaction of 3-Methyl-2-butenoic Acid (3a) with Butyllithium. A. Isomerization to 5a. Reaction of **3a** (2.50 g, 0.025 mol, mp 65–67 °C, lit.[6] mp 69.5–70 °C) in dry tetrahydrofuran (200 ml) with butyllithium [initially 0.050 mol of *n*- (2.5 M solution in hexane) or *tert*- (1.6 M solution in pentane) butyllithium] was carried out analogously to the general procedure described for **1**. Aliquots were quenched in water, made acidic, extracted with ether, concentrated, and analyzed by NMR. After 2 h of reaction in the presence of 2.0 equiv of butyllithium at −100 °C, a third molar equivalent of butyllithium was added to the reaction mixture at −100 °C and additional aliquots were examined (see Table II in discussion). The product acids **3a** and **5a** could not be separated by preparative GLC.

B. Reaction of the Lithio Derivative of 3a with Ethyl Iodide. Reaction of **3a** (2.50 g, 0.025 mol) in dry tetrahydrofuran (200 ml) with *n*-butyllithium (0.050 mol) and ethyl iodide (19.5 g, 0.125 mol) was carried out analogously to the procedure described in A for the preparation of **3c**. Concentration of the acid-containing organic extracts afforded 2.47 g of yellowish liquid. Analysis of this material by preparative GLC afforded analytically pure samples of the component acids [listed in order of their elution; the composition of a volatile fraction (7%) was not determined].

3-Methyl-2-butenoic acid (3a) (28%, 28% yield) was obtained as white needles [mp and mmp 65–67 °C, lit.[6] 69.5–70 °C; NMR ($CDCl_3$) δ 2.00 (s, 3, CH_3), 2.24 (s, 3, CH_3), 5.86 (m, 1, vinyl H), 12.0 (s, 1, OH)].

2-Ethyl-3-methyl-3-butenoic acid (8) (59%, 59% yield) was obtained as a colorless liquid [NMR ($CDCl_3$) δ 0.92 (t, 3, CH_2CH_3), 1.80 (s, 3, CH_3), 1.81 (m, 2, CH_2CH_3), 3.00 (t, 1, methine H), 5.00 (m, 2, *gem*-CH_2), 12.0 (s, 1, OH)].

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.75; H, 9.61.

2-Ethyl-3-methyl-2-butenoic acid (3c) (2%, 2% yield) was obtained as white needles (mp 42.5–44 °C, lit.[13] mp 49.5 °C; NMR data are reported above).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.41; H, 9.33.

(*E*)-3-Methyl-2-hexenoic acid (9) (2%, 2% yield) was obtained as white needles [mp 33.5–36 °C; NMR ($CDCl_3$) δ 0.94 (t, 3, $CH_2CH_2CH_3$) 1.56 (sextet, 2, $CH_2CH_2CH_3$), 2.19 (t, 2, $CH_2CH_2CH_3$), 2.20 (s, 3, CH_3), 5.82 (m, 1, vinyl H), 12.0 (s, 1, OH)].

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.57; H, 9.41.

2-*n*-Butyl-3-methyl-3-butenoic acid (10) (2%, 1% yield) was obtained as a colorless liquid [NMR ($CDCl_3$) δ 0.92 (t, 3, $CH_2CH_2CH_2CH_3$), 1.2–1.5 (m, 4, $CH_2CH_2CH_2CH_3$), 1.5–2.0 (m, 2, $CH_2CH_2CH_2CH_3$), 1.84 (s, 3, CH_3), 3.10 (t, 1, methine H), 5.02 (m, 2, *gem*-CH_2), 12.0 (s, 1, OH)].

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.30; H, 10.59.

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Registry No.—**1**, 1578-14-9; **2**, 60582-20-9; **3a**, 541-47-9; **3b**, 60582-29-8; **3c**, 60582-21-0; **3d**, 60582-22-1; **3e**, 60582-23-2; **3f**, 60582-24-3; **3g**, 60582-25-4; **3h**, 60582-26-5; **5a**, 1617-31-8; **8**, 60582-27-6; **9**, 27960-21-0; **10**, 60582-28-7; *n*-butyllithium, 109-72-8; *tert*-butyllithium, 594-19-4; ethyl iodide, 75-03-6; cyclohexanone, 108-94-1; benzophenone, 119-61-9; phenyl isocyanate, 103-71-9; dimethyl disulfide, 624-92-0; diphenyl disulfide, 882-33-7.

References and Notes

(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD128.
(2) This article is dedicated with deep appreciation to the late Professor Parham, deceased May 21, 1976.
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(5) The reaction mixture of **2** prepared as described in the Experimental Section was quenched in water after 15 min at −100 °C and the crude acids were isolated. The mixture of **3a** and **5a** thus obtained (in the ratio 95/5) could not be separated by recrystallization, sublimation, or GLC.
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(7) Sadtler Standard Infrared Grating Spectrum 677 K (melt).
(8) The reaction mixture of **2** prepared as described in the Experimental Section was quenched with excess CH_3OD (99% D); the crude product was contaminated with ~5% **3a** (deuterium content was not determined) and was purified by GLC.
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(11) GLC analyses were carried out on a column of 5% FFAP on 80/100 mesh Gas Chrom Q [6 ft × 0.25 in., 135 °C, 60 ml/min He (precoated support obtained from Applied Science Laboratories, P.O. Box 440, State College, Pa. 16801)].
(12) W. R. Purdum and C. J. Bartling, *J. Chem. Educ.*, **52**, 120 (1975).
(13) G. A. R. Kon et al., *J. Chem. Soc.*, **127**, 567 (1925).

Concerning the Significance of Product Development Control as an Important Factor in the Reduction and Alkylation of Model Ketone Systems

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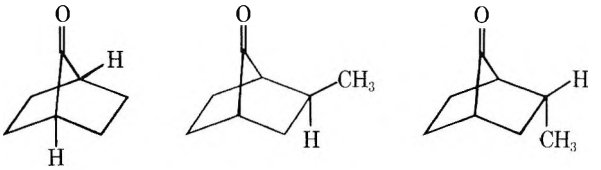
The concept of "product development control" has been used to explain the stereochemistry of many reactions in which the observed isomer ratio reflects the stability of the product. This concept has been used particularly to explain predominant formation of the most stable isomer in reactions of $LiAlH_4$ and MeMgBr with substituted cyclohexanones. A study of the reaction of $LiAlH_4$ and MeMgBr with 7-norbornanone and its *exo*-2-methyl and *endo*-2-methyl derivatives shows that the most unstable isomer is formed exclusively and hence product development control is not a factor in these reactions. In an attempt to broaden the scope of this study, three series of reagents were studied: (1) $LiBH_4$, $LiAlH_4$, and $LiGaH_4$, (2) BH_3, AlH_3, and GaH_3, and (3) $(CH_3)_2Be$, $(CH_3)_2Zn$, $(CH_3)_2Mg$, and $(CH_3)_3Al$. In no case was "product development control" observed. The reactions with the 7-norbornanone system are similar in nature to those with cyclohexanones, except that the complicating factors of torsional strain, compression effect, and conformational changes which are present in cyclohexanone systems are not present in the 7-norbornanone system. The concept of "product development control" is, therefore, a questionable one in ketone reductions involving $LiAlH_4$ and alkylations involving MeMgBr.

In recent years the area of stereoselective reduction and alkylation of ketones by metal hydrides and alkyls has received considerable attention.[1,2] All mechanisms concerning the stereoselective addition or reduction of ketones assume that the entering group approaches the carbonyl carbon on a line perpendicular to the plane of the carbonyl group so that maximum orbital overlap is achieved in the transition state. Dauben and co-workers[3] coined the terms "steric approach control" and "product development control" and suggested that these factors are important in determining the stereochemistry of $LiAlH_4$ reduction of cyclohexanones. Steric approach control implies an early, reactant-like transition state in which the entering group approaches the least hindered side of the ketone whereas product development control implies a late, product-like transition state in which the observed isomer ratio reflects the thermodynamic stability of the product.

The concept of "steric approach control" is generally agreed to be valid since certainly the ability of one molecule to approach another must depend to some extent on the steric requirements of the molecules involved. However, the concept of "product development control" has been questioned by Eliel and co-workers[4-7] on the basis of competitive rate studies involving $LiAlH_4$ and 3,3,5-trimethylcyclohexanone. They have shown that an axial methyl group in the 3 and/or 5 position retards the rate of axial attack compared to 4-*tert*-butylcyclohexanone, whereas the rate of equatorial attack remains essentially the same. This observation is not consistent with that predicted by "product development control" in that an axial methyl substituent would be expected to retard equatorial attack.

As an alternative to "product development control", Cherest and Felkin introduced the concept of "torsional strain"[8-11] and we have developed the concept of "compression effects" to explain the unusual stereochemistry observed in the reactions of $(CH_3)_3Al$ with substituted cyclohexanones.[12] The cyclohexanone ring system may also undergo conformational changes, a factor which has been discussed by Landor and Regan.[13] More recently orbital symmetry arguments[14] and unequal distortion of electron density[15] about the carbonyl group have been suggested to explain the stereochemistry of certain reactions.

Alkylation and reduction studies of a model ketone system in which torsional strain, compression effects, and conformational changes are not possible were carried out so that "steric approach control" and "product development control" could be evaluated independently of these other possible effects. 7-Norbornanone (I) exhibits bridgehead hydrogen atoms



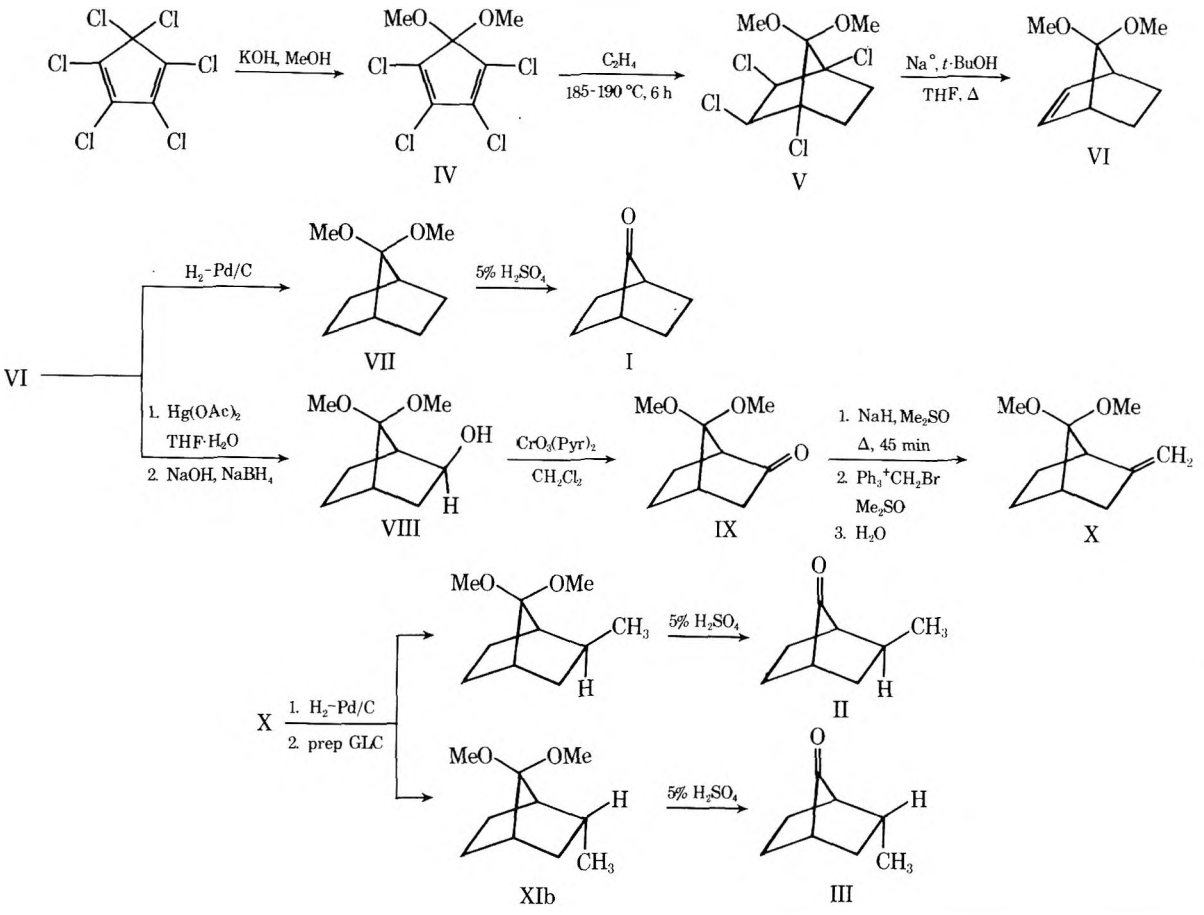
I II III

in the 1 and 4 positions which eclipse the carbonyl group in the 7 position. The unique feature, unlike that of the 2,6-diequatorial hydrogens in cyclohexanone which lie 4–5° below the plane of the carbonyl group, eliminates torsional strain or compression effect as a complicating factor in evaluating stereochemical data obtained from this system. The fact that I is a rigid bicyclic system further eliminates conformational changes in the substrate as a further complicating factor. It is clear then that the validity of the concept of "product development control" involving the reaction of $LiAlH_4$ or methylmagnesium bromide (Grignard reagents) as well as other reducing and alkylating reagents with ketones can be more rigorously tested using this system.

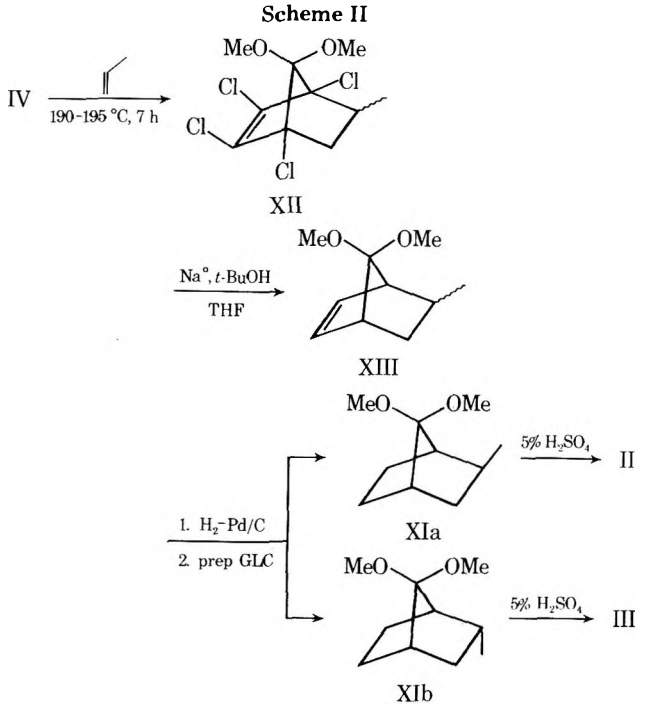
Results and Discussion

Synthesis of Model Systems for Reduction Studies. The synthesis of 7-norbornanone (I) was accomplished by the procedure of Gassman and Pape.[16] *exo*-2-Methyl-7-norbornanone (II) and *endo*-2-methyl-7-norbornanone (III) were prepared in a straightforward manner from 7,7-dimethoxy-2-norbornene (VI) (see Scheme I). Oxymercuration of VI led to an 80% yield of pure *exo*-2-hydroxy-7,7-dimethoxynorbornene (VIII) after distillation. Chromic acid oxidation of the alcohol in pyridine–dichloromethane afforded 7,7-dimethoxynorbornan-2-one (IX) in an 82% yield following distillation. This ketone was then converted to the corresponding methylene compound (X) using methyltriphenylphosphonium bromide and dimsyl sodium in dimethyl sulfoxide. Catalytic hydrogenation (X) gave a 7:1 ratio of II to III following 5% sulfuric acid catalyzed deketalization. The ketone and/or ketals were separated by gas–liquid chromatography on a 15 ft Carbowax 20M column. The NMR showed a chemical shift of δ 0.96 for II and δ 1.10 for III. These values agreed well with those reported previously.[17]

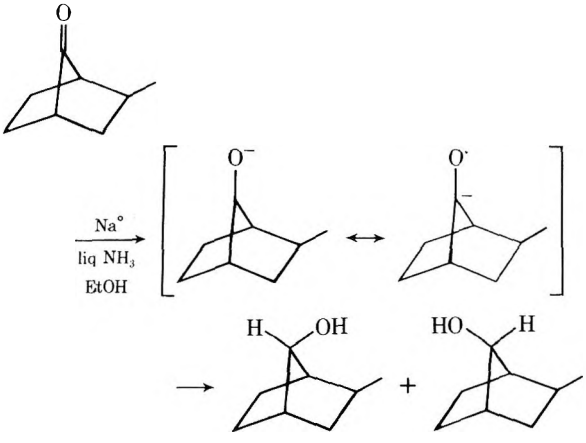
Scheme I



Scheme II



The reduction of ketones I, II, and III was carried out using $LiAlH_4$ as the reducing agent. For a summary of these results, see Table I. The presence of only one alcohol as the reduced product of ketone II was indicated by GLC and ^{13}C NMR. However, it was not possible to determine whether it was the syn or anti alcohol. Therefore, a Birch reduction on ketone II was conducted. Since protonation is faster than equilibration, both the syn- and anti alcohols should be produced (eq 1). It



(1)

was observed both by GLC and ^1H NMR that both the syn and anti alcohols were produced in a 20:80 ratio. The alcohols were separated by GLC and found to match the ^1H NMR spectrum reported in the literature.[18] Under Meerwein–Ponndorf–Verley reduction conditions using aluminum isopropoxide and isopropyl alcohol, only the anti alcohol from ketone II was produced. This indicates that under equilibrating conditions the anti alcohol is indeed the most thermodynamically stable product. In order to substantiate this, the syn alcohol was allowed to equilibrate under Meerwein–

An alternate route for the preparation of III was also accomplished as shown in Scheme II. Hexachlorocyclopentadiene was converted into 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (IV) as before. Propylene diluted with nitrogen was added to IV under Diels–Alder conditions giving 5-methyl-7,7-dimethoxy-1,2,3,4-tetrachloronorbornene (XII). XII was then dehalogenated in the presence of sodium metal to give 5-methyl-7,7-dimethoxynorborn-2-ene (XIII). Hydrogenation of XIII gave XIa and XIb in a 1:9 ratio. These ketals were then deketalized to give II and III in a 1:9 ratio.

Table I. Reactions of $LiAlH_4$ with Ketones I, II, and III in Diethyl Ether and THF[a]

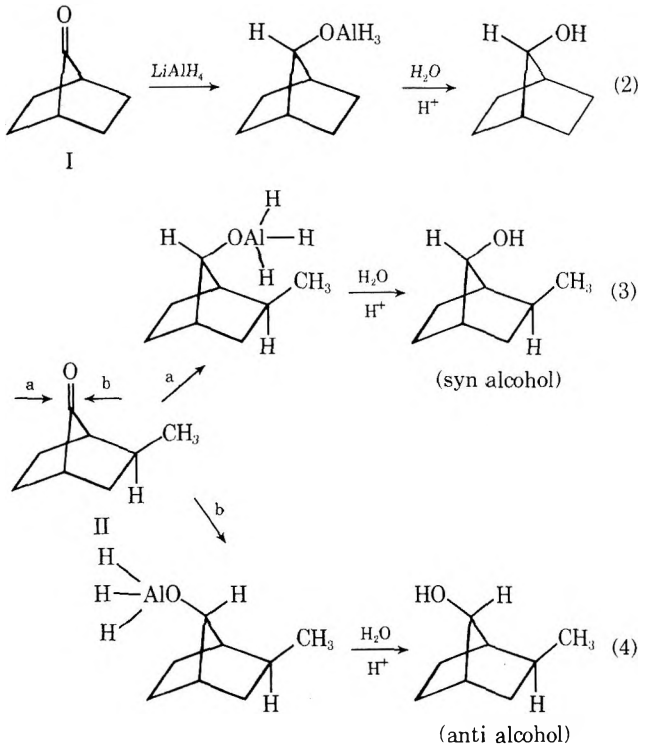
Run	Solvent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] H, OH	H, OH	OH	Mass balance
1	Et_2O	6			0			95.0			95.0
2	Et_2O		6			0			93.7		93.7
3	Et_2O			6			0			92.2	92.2
4	Et_2O	0.25	0.25		60.6	80.4		27.5	13.9		91.2
5	Et_2O	0.25		0.25	70.8		71.8	20.1		20.8	91.8
6	Et_2O		0.25	0.25		74.3	59.0		14.2	28.9	88.2
7	Et_2O	0.11	0.11	0.11	69.3	81.7	71.8	20.6	11.2	19.7	91.4
8	THF		6			0			94.3		94.3
9	THF		0.25	0.25		78.6	61.7		14.9	29.1	92.0
10	Et_2O		0.22	0.11		168.8	72.6		21.3	22.0	94.9
11	Et_2O		0.16	0.04		325.5	81.7		31.2	15.8	90.8
12	Et_2O		0.04	0.16		89.3	321.7		4.1	35.7	90.2

[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to $LiAlH_4$:ketone mole ratio of 1.5:1. [c] Percent of each ketone recovered based on 100% relative to the amount of hydride added. [d] Percent of each product based on 100% relative to the amount of hydride added.

Ponndorf conditions employing aluminum isopropoxide, isopropyl alcohol, and acetone. The anti alcohol was formed almost exclusively except for a trace of the syn alcohol thus further establishing that the anti alcohol is indeed the thermodynamic isomer.

The ^{13}C NMR spectra of the Birch reduction products were also obtained. By comparing these spectra with the reduction products of $LiAlH_4$ with ketone II, the latter product was confirmed as the syn alcohol. Carbon atom assignments were made by using relative shielding parameters and off-resonance coupling. It is known that deshielding of the carbon decreases from tetrasubstituted carbons to trisubstituted to disubstituted with monosubstituted carbons appearing furthest upfield.

Stereochemistry of 7-Norbornanone Reduction. The reaction of $LiAlH_4$ with I (eq 2) should produce the corresponding alcohol at twice the rate of $LiAlH_4$ reduction of II to produce the syn alcohol (eq 3) provided product development control is not important in this reaction. If product development control is important, then, of course, the rate of attack on II to produce the syn alcohol should be decreased owing to the effect of the *exo*-2-methyl group on the developing transition state (product development control).



Whether or not the *exo*-2-methyl group is sufficiently bulky to exert a valid test for product development control can be evaluated by comparing the syn–anti alcohol ratio when $LiAlH_4$ is allowed to react with II. If the *exo*-2-methyl group exerts a significant steric effect in this system then significally less anti alcohol (eq 4) should be produced compared to the syn alcohol in the reaction of II with $LiAlH_4$. In order to test pertubations on the carbonyl group other than the steric effect exerted by the *exo*-2-methyl group, the reaction of $LiAlH_4$ with *endo*-2-methyl-7-norbornanone (*III*) was also studied. If only the steric effect of the *exo*-2-methyl group is significant, then the reaction of $LiAlH_4$ with III to produce the syn and anti alcohol should proceed at the same rate as the reaction of $LiAlH_4$ with I and at twice the rate compared to the formation of the *syn*-2-*exo*-methyl alcohol.

The reductions of I, II, and III were carried out under identical conditions. As noted before, only one reduction product was obtained for I and II, whereas III gave both the syn and anti alcohols according to GLC and ^{13}C NMR. By comparing GLC and ^{13}C NMR, it was substantiated that the lone reduction product of II was the syn alcohol. Table I shows these observations as a result of anti attack with respect to the *exo*-2-methyl group. This shows that the *exo*-2-methyl group exerts a significant steric effect with respect to attack at the 7-keto group since no anti alcohol is observed. When I and II were admixed in equal molar portions with an insufficient amount of $LiAlH_4$, the alcohol products of I and II were produced in a 2:1 ratio indicating no detectable product development control. Reaction of I and III in equal molar portions with an insufficient amount of $LiAlH_4$ produced the corresponding alcohols in a 1:1 ratio showing that the *endo*-2-methyl group has no effect on the rate of reaction of the 7-keto group. Admixture of II and III in equal molar ratio produced the corresponding alcohols in a 1:2 ratio and admixture of I, II, and III in equal molar ratio produced the corresponding alcohols in a 2:1:2 ratio when allowed to react with an insufficient amount of $LiAlH_4$. The data support the conclusion that anti attack on II takes place at the same rate as attack from either side of the carbonyl on I and III indicating that the exo-2-methyl group, although exerting a significant steric

Table II. Reactions of MH_3 with Ketones I, II, and III in Diethyl Ether[a]

Run	Reducing agent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] H OH	H OH	OH	Mass balance
1	BH_3		6			0			95.2		95.2
2	BH_3		0.25	0.25		71.8	55.5		15.7	29.3	86.1
3	AlH_3		6			0			96.3		96.3
4	AlH_3		0.25	0.25		70.9	62.7		15.8	30.4	90.0
5	GaH_3		6			0			94.7		94.7
6	GaH_3		0.25	0.25		69.7	54.3		18.0	35.9	89.2

[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to metal hydride:ketone mole ratio of 2:1. [c] Percent of each ketone recovered based on 100% relative to the amount of hydride added. [d] Percent of each product based on 100% relative to the amount of hydride added.

Table III. Reactions of Complex Metal Hydride of Varying Anion Size with Ketones II and III in THF[a]

Run	Reducing agent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketones, % I	II	III	Products[d] H OH	H OH	OH	Mass balance
1	$LiBH_4$		6			0			97.2		97.2
2	$LiBH_4$		0.25	0.25		73.5	60.2		15.7	32.0	90.7
3	$LiAlH_4$		6			0			94.3		94.3
4	$LiAlH_4$		0.25	0.25		78.6	61.7		14.9	29.1	92.0
5	$LiGaH_4$		6			0			94.5		94.5
6	$LiGaH_4$		0.25	0.25		75.3	58.5		12.9	25.5	86.3

[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to complex metal hydride:ketone mole ratio 1.5:1. [c] Percent of each ketone recovered based on 100% relative to the amount of hydride added. [d] Percent of each product based on 100 percent relative to the amount of hydride added.

Table IV. Reactions of Complex Metal Hydrides of Varying Cation Size with Ketones II and III[a]

Run	Reducing agent	Solvent	Ratio[b] hydride:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] H OH	H OH	OH	Mass balance
1	$LiAlH_4$	THF		6			0			94.3		94.3
2	$LiAlH_4$	THF		0.25	0.25		78.6	61.7		14.9	29.1	92.0
3	$NaAlH_4$	THF		6			0			95.7		95.7
4	$NaAlH_4$	THF		0.25	0.25		75.9	59.3		14.7	27.2	89.2
5	NR_4AlH_4	THF–benzene		6			0			94.6		94.6
6	NR_4AlH_4	THF–benzene		0.25	0.25		76.4	58.3		13.6	26.1	87.5

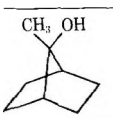
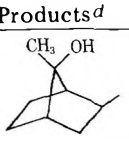
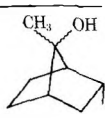
[a] The hydride was added to 0.032 mmol of ketone at 25 °C for 2 h. [b] Hydride:ketone = 6 is equivalent to complex metal hydride:ketone mole ratio 1.5:1. [c] Percent of each ketone recovered based on 100% relative to the amount to hydride added. [d] Percent of each product based on 100% relative to the amount of hydride added.

effect (no anti *exo*-2-methyl alcohol formed, eq 4), does not affect the formation of the syn alcohol of II. When the mole ratio of II to III was increased from 1:1 to 2:1 in the presence of an insufficient amount of $LiAlH_4$ the corresponding alcohols produced were in a ratio of 1:1. This can be explained by the fact that there are now the same number of equal attack sites on both II and III. When the mole ratio of II:III was 4:1, the number of equal attack sites becomes 2:1, and this is indicated by the observation that the ratio of alcohols is 2:1. On the other hand, when the ratio of II:III was 1:4, the number of equal attack sites is 1:8, which is what is reflected in the results of this experiment (Table I). Further experiments in THF and at different stoichiometric ratios provide additional evidence for the above conclusions.

Table II compares the group 3A metal hydrides, AlH_3, BH_3, and GaH_3, reactions with ketones II and III. The results are similar to those observed for $LiAlH_4$ reduction indicating that the stereochemistry is independent of the steric requirement of the hydride. Similarly, when $LiBH_4$, $LiAlH_4$, and $LiGaH_4$ were allowed to react with ketones I–III, no evidence of "product development control" was observed (Table III). In addition when the anion (AlH_4^-) was held constant and the cation varied (Li, Na, NR_4), no evidence of "product development control" was observed (Table IV).

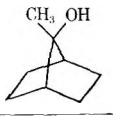
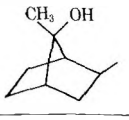
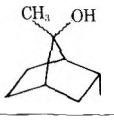
Synthesis of Model Systems for Alkylation Studies. Alkylations of ketones I, II, and III were carried out using methylmagnesium bromide in diethyl ether in an attempt to evaluate the importance of "product development control" when ketones are allowed to react with organometallic alkylating agents. For a summary of these results see Table V. Identification of the products of these reactions is essential just as in the case of the reduction study. The alkylation of ketone II produced only one product as was verified by GLC, ^1H NMR, and ^{13}C NMR. Assuming that the lone alkylation

Table V. Reactions of Methylmagnesium Bromide with Ketones I, II, and III[a]

Run	Solvent	Ratio[b] methyl:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] 			Mass balance
1	Et_2O	6			0			90.3			90.3
2	Et_2O		6			0			95.4		95.4
3	Et_2O			6			0			89.8	89.8
4	Et_2O	0.25	0.25		59.7	78.4		28.3	13.8		90.1
5	Et_2O	0.25		0.25	69.5		70.3	21.2		20.8	90.9
6	Et_2O		0.25	0.25		82.6	63.8		14.9	30.7	96.0
7	Et_2O	0.11	0.11	0.11	70.2	81.0	71.0	20.1	10.8	19.7	90.9
8	Et_2O		0.22	0.11		173.1	76.3		19.8	19.1	96.1
9	Et_2O		0.16	0.04		322.5	82.3		30.6	16.0	90.3
10	Et_2O		0.04	0.16		90.2	330.6		4.4	36.2	92.3
11	THF		0.25	0.25		80.7	61.8		14.2	29.3	93.0
12	THF		6						93.4		93.4

[a] The alkylating agent was added to 0.032 mmol of ketone at 25 °C for 1 h. [b] Methyl:ketone = 6 is equivalent to RMgX:ketone ratio of 6:1. [c] Percent of each ketone recovered based on 100% relative to the amount of alkylating agent added. [d] Percent of each product based on 100% relative to the amount of alkylating agent added.

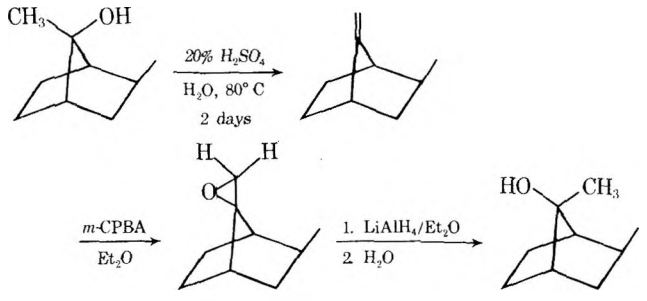
Table VI. Reactions of Metal Alkyls of Varying Steric Requirement with Ketones II and III in Diethyl Ether[a]

Run	Reducing agent	Ratio[b] methyl:ketone I	II	III	Recovered[c] ketone, % I	II	III	Products[d] 			Mass balance
1	Me_2Be		6			0			95.3		95.3
2	Me_2Be		0.25	0.25		83.4	64.3		15.4	31.1	97.1
3	Me_2Mg		6			0			94.6		94.6
4	Me_2Mg		0.25	0.25		80.7	60.1		17.1	33.3	95.6
5	Me_2Zn		6			0			67.3		67.3
6	Me_2Zn		0.25	0.25		65.3	42.8		11.2	20.4	69.8
7	Me_3Al		6[e]			0			65.3		65.3
8	Me_3Al		0.25[e]	0.25[e]		60.2	40.7		10.3	19.6	65.4

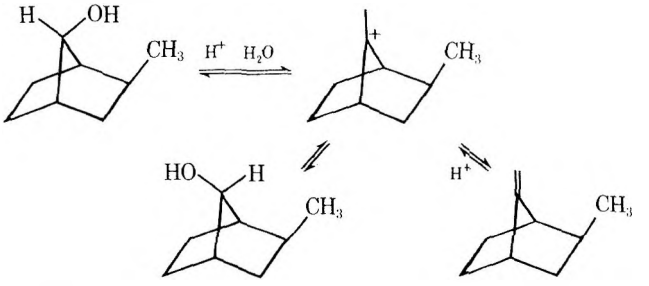
[a] The alkylating agent was added to 0.032 mmol of ketone at 25 °C for 1 hr. [b] Methyl:ketone = 6 is equivalent to R_2M:ketone mole ratio of 3:1. [c] Percent of each ketone recovered based on 100% relative to the amount of alkylating agent added. [d] Percent of each product based on 100% relative to the amount of alkylating agent added. [e] Methyl:ketone = 6 is equivalent to Me_3Al:ketone mole ratio of 2:1.

product was the syn alcohol, the anti alcohol had to be synthesized. A straightforward method to produce the anti alcohol was carried out according to Scheme III. The first step

Scheme III



in this sequence was to dehydrate the tertiary alcohol to the methylene compound followed by epoxidation by *m*-chloroperbenzoic acid which is then followed by $LiAlH_4$ reduction to yield the anti alcohol. However, after periodic monitoring by GLC, it was noted that a second peak appeared with a longer retention time than the starting "syn" alcohol. This second peak continued to grow until it was approximately ⅓ of the starting reactant. This newly formed compound was separated by GLC and identified by ^1H NMR and ^{13}C NMR. By comparing shielding parameters, as was done for the reduction products identification, this second compound was identified as the anti alcohol. The following sequence is postulated to have taken place.



Stereochemistry. The alkylations of I, II, and III were carried out under identical conditions. As noted for the reduction reactions, only one alkylation product was obtained for ketones I and II, whereas ketone III gave both the syn and anti alcohol according to GLC, ^1H NMR, and ^{13}C NMR. Table V shows the results of the alkylation studies with methylmagnesium bromide. In Table VI are recorded the observations of metal alkyl reactions with ketones II and III. Both tables show essentially the same results as noted for the reductions studies conducted with the same ketones. That is, the *exo*-2-methyl group exerts a significant steric effect with respect to attack at the 7-keto group since no anti alcohol is observed. Also, anti attack on II takes place at the same rate as attack from either side of the carbonyl on I or III indicating

that the *exo*-2-methyl group does not affect the formation of the syn alcohol of II. Therefore it can be concluded that product development control in the alkylation reactions of this model ketone system is not important compared to steric approach control.

Experimental Section

Materials. Fisher reagent grade anhydrous diethyl ether was distilled under nitrogen from $LiAlH_4$ prior to use. Fisher reagent grade tetrahydrofuran (THF) was distilled under nitrogen from $NaAlH_4$ prior to use. Hexachlorocyclopentadiene was obtained from Aldrich Chemical Co. and used without further purification.

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (IV). Hexachlorocyclopentadiene was converted to IV with methanolic potassium hydroxide according to McBee's procedure.[19]

7,7-Dimethoxy-1,2,3,4-tetrachloronorborn-2-ene (V). Under Diels–Alder conditions according to the procedure of Gassman,[16] IV was converted to V with a mixture of ethylene and nitrogen.

7,7-Dimethoxynorbornene (VI). According to the procedure of Gassman and Marshall,[20] V was converted to VI by direct sodium dechlorination.

7-Norbornanone (I). The procedure of Gassman and Pape[16] was followed for the preparation of I which involves the hydrogenation of VI using a palladium on carbon catalyst followed by deketalization using 5% H_2SO_4 or glacial acetic acid to yield I.

***exo*-7,7-Dimethoxynorbornan-2-ol (VIII).** A 500-ml round-bottom flash equipped with a magnetic stirrer was charged with 12.76 g (0.04 mol) of mercuric acetate followed by 40 ml of water. The mercuric acetate dissolved to give a clear solution. Tetrahydrofuran (40 ml) was added to the solution forming a bright yellow suspension. To the mixture, which was cooled in an ice bath, was added 0.038 mol of VI with stirring. The mixture was allowed to warm to room temperature with stirring until the reaction mixture became colorless and clear (30 min). Stirring was continued for an additional 15 min and 40 ml of 3 M sodium hydroxide was added followed by 40 ml of 0.5 M sodium borohydride in 3 M sodium hydroxide. The reduction was almost instantaneous. The mercury was then allowed to settle, and the water layer saturated with sodium chloride. The tetrahydrofuran layer was separated, dried with anhydrous sodium sulfate, and filtered, after which the solvent was removed by rotary evaporation. The crude product was distilled to give 0.030 mol (5.2 g) (79.9%), bp 88–91 °C (6–7 mm).

7,7-Dimethoxynorbornan-2-one (IX). A solution of 16.5 g (0.096 mol) of VIII in 20 ml of dry methylene chloride was added with stirring to the complex formed from 10 g of chromium trioxide and 100 ml of dry pyridine in 100 ml of methylene chloride.[21] After stirring for 2 h, the solvent was decanted and removed by rotary evaporation. The crude product was distilled to yield 13.3 g (0.078 mol), 81.7%, bp 71–72 °C (1–2 mm).

2-Methylene-7,7-dimethoxynorbornane (X). A solution of sodium methylsulfinyl carbanion was prepared according to the procedure of Corey.[22] Into a three-necked, round-bottom flask was placed 3.84 g (0.08 mol) of sodium hydride (50% mineral oil dispersion). The sodium hydride was washed three times with petroleum ether by swirling, allowing the hydride to settle, and decanting the liquid portion in order to remove the mineral oil. The flask was immediately fitted with a magnetic stirrer, a reflux condenser, and a pressure-equalizing dropping funnel. A three-way stopcock, connected to the top of the reflux condenser, was connected to a water aspirator and a source of dry nitrogen. The system was evacuated until the last traces of petroleum ether were removed from the sodium hydride and was then flushed with nitrogen by evacuating and filling the nitrogen several times. The aspirator hose was removed and this arm of the stopcock was connected to a bubbler to which the system is opened. Dimethyl sulfoxide which was distilled from calcium hydride (bp 64 °C, mm) was introduced through the dropping funnel and the mixture was heated with stirring to 70–75 °C until the evolution of hydrogen ceases, which usually was about 45 min. The solution was cooled in a cold water bath and stirred during the addition of 17.8 g (0.077 mol) of (methyl)triphenylphosphonium bromide in 50 ml of warm dimethyl sulfoxide whereupon the deep red color of the ylide was produced. After stiring for 15 min the ketone IX in 10 ml of dimethyl sulfoxide was added with stirring in a cold water bath. The reaction mixture was heated to 60 °C for 4 h. The reaction mixture was then cooled and poured into 500 ml of cold water. The mixture was extracted three times with pentane, washed once with water, dried over anhydrous sodium sulfate, and the solvent removed by rotary evaporation. The crude product was distilled to give 10.0 g (0.06 mol), 77% yield, bp 76–80 °C (15 mm).

2-Methyl-7,7-dimethoxynorbornane (XI). In a hydrogenation flask, X was added to 10 ml of 95% ethanol and 0.3 g of 5% palladium on carbon. This mixture was stirred under hydrogen at room temperature until the amount of hydrogen (1344 ml) had been taken up. The catalyst was removed by filtration, and the crude product was purified and the exo and endo isomers were separated by preparative gas chromatography using a 6 ft × 0.5 in. i.d. 20% Carbowax 20M on Chromosorb W-NAW at 125 °C with a flow rate of 6.5 cm^3/min. The exo ketal XIa was in a ratio of 7:1 with the endo ketal XIb.

***exo*-2-Methyl-7-norbornanone (II).** Into a 50-ml Erlenmeyer flask, the exo ketal XIa was added to 25 ml of 5% H_2SO_4 and stirred for 12 h. The crude ketone was purified by GLC. The ^1H NMR showed a doublet at δ 0.96, J = 6 Hz.

***endo*-2-Methyl-7-norbornanone (III).** The same procedure used above for the preparation of the exo ketone was incorporated in the preparation of III.

5-Methyl-7,7-dimethoxy-1,2,3,4-tetrachloronorborn-2-ene (XII). A mixture of propylene and nitrogen was bubbled into 264 g of IV which had been preheated to 190 °C. After maintaining these conditions for 6 h, the reaction mixture was cooled and distilled to give 229.5 g (75%) of XII, bp 88–91 °C (0.7 mm).

5-Methyl-7,7-dimethoxynorborn-2-ene (XIII). To a vigorously stirred solution of 90 g (1.22 mol) of *tert*-butyl alcohol, 525 ml of dry tetrahydrofuran, and 59 g (2.57 g-atoms) of finely chopped sodium metal under a nitrogen atmosphere was added 30.6 g (0.1 mol) of XII. The mixture was heated gently to maintain a steady reflux for 10 h. After cooling, the excess sodium was destroyed by slow addition of methanol (about 500 ml) to the reaction mixture. The reaction mixture was poured over 2 l. of ice and the reaction flask was washed with approximately 600 ml of water. The solution was extracted with three 250-ml portions of water and once with saturated sodium chloride solution. The ethereal solution was dried over anhydrous sodium sulfate and filtered. The crude product was distilled to give 9.8 g (58.7%), bp 73–78 °C (13 mm).

Hydrogenation of XIII. In a hydrogenation flask, 9.8 g of XIII was added to 10 ml of 95% ethanol and 0.10 g of 5% palladium on carbon. This mixture was stirred under hydrogen at room temperature. After the hydrogen absorption had ceased, the catalyst was removed by filtration. The crude product was purified and the exo and endo isomers were separated by preparative GLC yielding a 9:1 ratio of endo and exo ketals. The spectra of these compounds were identical with those of the exo and endo ketals XIa and XIb prepared above.

Birch Reduction of II. To a 100-ml three-necked round-bottom flask equipped with a magnetic stirrer, dry ice–acetone condenser, and a stopper were added 50 ml of condensed anhydrous ammonia, 0.122 g (0.001 mol) of II, and 2.5 ml of absolute ethanol. To this stirred reaction mixture, 0.7 g of finely chopped sodium metal was added. A deep blue color was produced. Stirring was continued for 15 min and the ammonia allowed to evaporate after the addition of 2.5 ml of water. The mixture was extracted twice with hexane. The combined hexane extracts were washed with water and saturated sodium chloride solution and then dried with anhydrous sodium sulfate. The hexane was removed by rotary evaporation. The residue showed two peaks on the gas chromatograph using a 15-ft, 20% Carbowax 20M on Chromosorb W-NAW column which indicated the syn and anti alcohols in a 20:80 ratio. The syn alcohol has the shorter retention time compared to the anti alcohol. The first alcohol eluting off the column matched the retention time of the alcohol obtained from the reduction of II by $LiAlH_4$. See the Discussion. Also, the ^1H NMR showed two absorptions at δ 4.10 and 3.97—a 20:80 ratio. This together with ^{13}C NMR confirmed that the major product of the Birch reduction of II was the anti alcohol.

Complex Metal Hydride Reductions. A 50-ml Erlenmeyer flask equipped with a magnetic stirring bar was flash flamed under nitrogen and then fitted with a rubber septum. The flask was cooled to 0 °C and 1 ml of 0.032 M ketone in tetrahydrofuran or diethyl ether was added to the flask, along with the internal standard which was hexadecane. The reactions were quenched after 2 h with saturated ammonium chloride and the solvent partially removed under vacuum (Tables I–IV).

Meerwein–Ponndorf–Verley Reduction (II). Into a 50-ml flask fitted with a partial reflux head and a magnetic stirrer were placed 2 ml of a 0.032 M solution of II in diethyl ether along with 1.0 g of aluminum isopropoxide and 5 ml of isopropyl alcohol. This mixture was heated to 50 °C and stirred for 2 days. After cooling to room temperature, the mixture was poured into 100 ml of saturated aqueous ammonium chloride and the solution extracted with two 10-ml portions of ether. The ethereal extracts were combined, washed with water and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The ether was partially removed by use of a

water aspirator. This solution was then analyzed as before by GLC. The only product was the anti alcohol.

Meerwein–Ponndorf Equilibration of II and III. Into a 50-ml round-bottom flask equipped with a magnetic stirrer were placed 100 mg of *syn*-2-*exo*-methyl-7-norbornanol, 1 g of aluminum isopropoxide, 5 ml of isopropyl alcohol, and 5 ml of acetone. Mild heat was applied with stirring for 3 days. The GLC analysis of the hydrolyzed mixture showed the anti alcohol almost exclusively except for a trace of the syn alcohol.

Alkylations of I, II, and III. The same procedure used for the reductions was invoked for the alkylations. All of the products were isolated and identified via ^{1}H NMR, ^{13}C NMR, and GLC.

Acknowledgment. We wish to thank the National Science Foundation for support of this work.

Registry No.—I, 10218-02-7; II, 59532-17-1; III, 59532-18-2; IV, 2207-27-4; VI, 875-04-7; VIII, 10421-72-4; IX, 10265-39-1; X, 60761-81-1; XIa, 60734-22-7; XIb, 60734-23-8; XII, 60734-24-9; XIII, 60734-25-0.

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Thermal and Base-Catalyzed Isomerizations of Birdcage and Half-Cage Compounds

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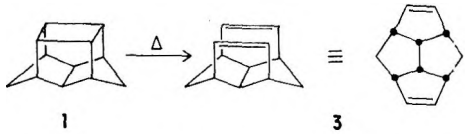
Thermal rearrangements of the birdcage hydrocarbon and alcohol afforded a novel, all-cis fused tetracyclic system containing four five-membered rings. Base-promoted isomerizations of the birdcage alcohol and the half-cage ketone proceeded via a transannular keto–enolization process involving a γ hydrogen to give a new isomeric half-cage ketone.

The birdcage and half-cage compounds[1] have provided attractive frameworks for the study of transannular interactions and for further synthetic investigations.[2] Here, we report new polycyclic systems obtained by thermal and base-promoted[3] isomerizations of these systems.

Thermal Isomerization. Thermal behavior of the birdcage hydrocarbon (**1**) and its derivatives was initially studied over heated quartz chips using a pyrolytic gas chromatogram unit. Hydrocarbon **1** was stable below 500 °C but between 500 and 650 °C it afforded a mixture of **1** and a new hydrocarbon **3**.[4]



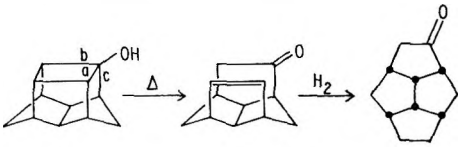
1 **3**

4 **5**

Above 700 °C complete degradation to small fragments resulted. Under preparative conditions over silicon chips, compound **3** was obtained in 27% yield (35% conversion) at 600 °C. No isomerization occurred at 550 °C, and at 650 °C the yield of **3** was about one-half that at 600 °C due to extensive fragmentation. Over platinum, extensive decomposition occurred above 500 °C and naphthalene was the sole identifiable product.

The diene **3** is an air-sensitive, colorless wax, mp 134–136 °C, and the mass spectral fragmentation pattern closely resembled that of **1**. The UV spectrum showed only end absorption. The infrared spectrum contained typical cyclopentene bands[2] at 3040, 1615, and 725 cm^{-1} but was significantly different from that of the isomeric diene **4** (3020, 1566, and 725 cm^{-1}). The ^{1}H NMR spectrum showed a sharp singlet at δ 5.40 (4 H) due to olefinic protons and two broad singlets at 1.95 (4 H) and 3.37 (6 H) due to secondary and tertiary protons, respectively. The diene **3** absorbed 2 mol of hydrogen to give an air-stable, tacky hydrocarbon **5**.

The birdcage alcohol **2** rearranges more readily than **1**. Scouting pyrolysis experiments indicated that **2** rearranged cleanly between 255 and 400 °C to unsaturated ketone **6**.



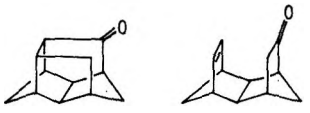
2 **6** **7**

Between 500 and 600 °C the pyrolysate contained another ketone which had the same retention time and ir as the iso-half-cage ketone **8** (see below), as well as smaller fragments. Above 700 °C complete decomposition was observed. Preparatively **6** was obtained in 79% yield (91% conversion) by feeding an alcoholic solution of **2** over silicon chips at 500 °C. The unsaturated ketone **6** was, like **3**, air sensitive and satisfactory elemental analyses were difficult to obtain. Compound

6 readily absorbed 1 mol of hydrogen to give 7 and formed air-stable carbonyl derivatives such as the oxime and tosylhydrazone. Thermal decomposition of the tosylhydrazone sodium salt afforded the diene 3.

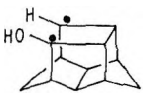
It has been reported[1e] that the diene 4 can be transformed to 1 photochemically or thermally in the presence of traces of acid. Thus, the present study demonstrates a conversion of the highly strained diene 4 to the practically strain-free diene 3 through the birdcage structure. The double bond stretching frequencies of 3 and 4 clearly reflect strains involved in these ring systems. Furthermore, Dreiding models show that 3 is much more flexible and open than 4. The two double bonds are separated by more than 4 Å in 3, whereas those in 4 are rigidly held within the van der Waals distance. Although the present results suggest high regiospecificity in the thermal reorganization of 3, formation of 4 cannot be totally discounted since it might have rearranged[1e] in our GLC system.

Thermal reorganization of 2, on the other hand, is definitely regiospecific in the direction of the least strained ketone 6. The carbonyl frequencies of 6 (1735 cm^{-1}) and the isomeric ketone 9[2] (1742 cm^{-1}) again reflect angle strains in the ring systems.



8 9

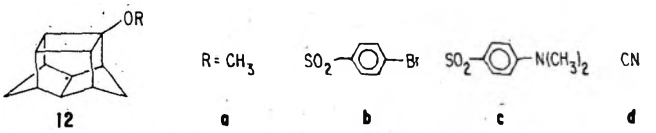
The saturated ketone 7 shows the stretching at 1730 cm^{-1} as does perhydrotriquinacenone.[5] Lack of C–H stretching above 3000 cm^{-1} in the saturated ketone 7 and hydrocarbon 5 further indicates the absence of transannular hydrogen repulsion.[1d] Thermal reorganizations of cyclobutanols[6] have been accounted for by the intermediate formation of 1,4-hydroxy-1,4-diradicals followed by (1) further bond cleavage to give ketone and olefin, (2) hydrogen migration to ketone, and (3) ring closure to the starting material and its stereoisomers. These three processes are generally competitive and, in the case of unsymmetric cyclobutanols, they proceed with two different 1-hydroxy-1,4-diradicals.[6b] Although the thermal reorganization of 2 is in general accord with the above mechanism, it should be pointed out that we have isolated products only from the diradical 10 generated by cleavage of the bond a in 2. No products from bond cleavage at b or c were detected. Furthermore, 10 fragments preferentially to give 6, and hydrogen migration to form ketone 8 competes only above 500 °C.



10

Although 1-hydroxy-1,4-diradicals have never been detected spectrophotometrically,[7] it is well documented[8] that the Norrish type II photoreaction of ketones having γ hydrogens generates 1-hydroxy-1,4-diradicals which behave as do thermally generated diradicals.[6] Irradiation of the half-cage ketone 8 or 11 in cyclohexane, however, resulted in a complete recovery of the starting material either in the presence or in the absence of a sensitizer, benzophenone. The failure of these ketones to undergo the photoreaction may be attributed to unfavorable spacial disposition of the γ hydrogens with respect to the half-filled n orbital of the n–π* excited carbonyl group.[8b] Thermally, these ketones decompose above 600 °C without prior isomerization.

Whereas thermal reorganization of 2 took place more readily than that of 1, the methoxy derivative 12a did not isomerize below 450 °C and decomposed completely above 500 °C. There is no obvious explanation for the greater thermal

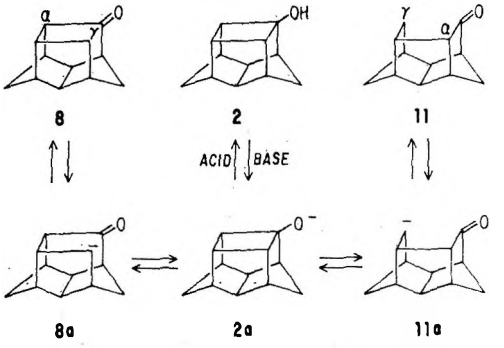


12 a b c d

stability of 12a as compared to 2, since a methoxy group is expected to stabilize the adjacent carbon radical center by 2–3 kcal/mol relative to a hydroxyl group.[9]

Since cage amines show interesting biological activities[10] and since the birdcage *p*-bromobenzenesulfonate 12b has been reported[11] to solvolyze to unrearranged acetate in acetic acid containing sodium acetate, we have attempted to prepare the birdcage amines by carbonium ion processes. Treatment of 12b with dimethylamine at 200 °C, however, afforded the *p*-dimethylaminobenzenesulfonate 12c. The cyanate 12d was recovered even after distillation at atmospheric pressure in the absence or presence of anhydrous ferric chloride. Rearrangement to the corresponding isocyanate[5,12] could not be accomplished either by acidic alumina or Lewis acids. Treatment of 2 with acetonitrile in the presence of sulfuric acid (Ritter reaction) also failed to give the corresponding acetamide.

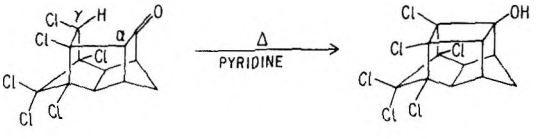
Transannular Keto–Enol Isomerization. In contrast to the thermal rearrangement, the birdcage alcohol[11] 2 rearranged[3] in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide at 250 °C to give a mixture of two ketones in approximately 96:4 ratio (GLC analysis). A mixture of virtually identical composition was obtained when the half-cage ketone 11[1d] was subjected to similar treatment. The major



8 2 11

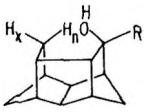
8a 2a 11a

product was identified as the isomeric half-cage ketone 8 based on chemical and spectral evidence and the minor component as the starting material 11 by GLC peak matching. Howe and Winstein[3b] found that the isomerization of 11 was first order in its disappearance at 175–200 °C and that homoketonization of 2a proceeded ca. 33 000 times faster than the isomerization of 11 at 100 °C. Under these conditions they observed no homoketonization in the direction of 11. There is no doubt, however, that the isomerization of 11 to 8 involves the transannular enolate 2a common to both ketones 8 and 11. Base-catalyzed transannular ketonization of bridged alcohols can proceed with a high degree of stereoselectivity, and both retention[13] and inversion[14] of configuration have been reported depending upon the ring system. Recently, Crow and Borden[15] found through deuterium labeling studies that the opening of 2 to 8 proceeded with 95 ± 3% retention of configuration in *tert*-butyl alcohol-*d*, the solvent delivering the endo proton at C-γ in 8. Although the stereochemistry of the transformation between 2 and 11 has not been studied, the facile conversion of the hexachloro compound 13 to 14 in re-



13 14

fluxing pyridine[11] points also to an endo-proton abstraction. Treatment of the half-cage ketone 11 with stronger and more nucleophilic bases like *n*- and *tert*-butyllithium as well as lithium aluminum hydride afforded O-inside alcohols 15 with



15a R = H
15b R = n-C_4H_9
15c R = t-C_4H_9

15

high degrees of stereoselectivity but no transannular enolization process was observed.

Thus, the base-catalyzed homoketonization of 2 proceeded predominantly to give the less strained ketone 8. Difference in steric hindrance about the carbonyl group of 8 and 11 was demonstrated, dramatically, by their reactivities toward hydroxylamine. Whereas 8 could be converted to oxime 14 under normal conditions, 11 did not react even under 10 000 atm at 75 °C; under these conditions di-*tert*-butyl ketone is reported to give the corresponding oxime in 96% yield.[16] In accord with these results, alcohol 15 showed a sterically compressed, high frequency stretch near 3080 cm^{-1}, whereas the endo alcohol[3b] derived from ketone 8 is reported to show no absorption above 3000 cm^{-1}.

Although the syntheses of 1 and 2 have been described previously,[1] the improved and large-scale preparations are included in the Experimental Section.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer as potassium bromide pellets, unless otherwise noted. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer on solutions in 95% ethanol, unless otherwise noted. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 spectrophotometer (60 MHz), unless indicated otherwise, on solutions (10–40%) in deuteriochloroform, with chemical shifts reported in parts per million downfield from an external standard of tetramethylsilane, and with coupling constants in hertz. Melting points and boiling points were uncorrected.

Pyrolysis. A. In pyrolysis studies using a pyrolytic gas chromatogram unit, approximately 15 mg of a solid sample or 10 μl of ca. 50% solution was injected into a preheated part of a pyrolysis tubing filled with 20 mesh quartz chips maintained at various temperatures. The pyrolysate was directly introduced into a gas chromatogram unit and each peak was separately collected for spectral analysis.

B. In preparative scale pyrolysis, a quartz pyrolysis tube, 28 cm × 1.6 cm i.d., was packed with 30 mesh silicon chips and was heated by nichrome ribbon which was wound around the tube and insulated with asbestos. A thermocouple was placed at the hottest point in the tube—about one-half the way down. Temperature was recorded and maintained with a Brown Pyr-O-Vane. The pyrolysis tube was surmounted either by a jacketed vapor feeder or by a specially designed dropping funnel. The vapor feeder permitted the substrate to be carried by a stream of nitrogen directly into the pyrolysis tube in the vapor state, the temperature for vaporization being maintained by reflux of the appropriate solvent in the jacket of the feeder. The dropping funnel was designed to permit simultaneous flow of the liquid charge and the carrier gas (nitrogen) directly into the tube. The exit from the pyrolysis tube led directly into a dry ice trap where the pyrolysate was condensed.

Pyrolysis of Birdcage Hydrocarbon. A. A solid sample or pentane solution of 1 was pyrolyzed in the pyrolytic gas chromatogram unit and the pyrolysate was analyzed on a 6 ft × 0.25 in. o.d. copper column packed with 20% silicon grease on 35–48 mesh Chromosorb P at 168 °C and 100 ml/min helium flow. Below 500 °C the pyrolysate showed a single peak at 8.6 min due to 1 (confirmed by the ir and mass spectra). Between 500 and 650 °C, a new peak appeared at 9.4 min. The IR, NMR, and mass spectra of this material were practically identical with those of an analytical sample of 3 (see below). Above 700 °C complete fragmentation was observed. The optimum temperature for 3 was 600 °C and the products consisted of approximately equal amounts of 1 and 3.

B. The birdcage hydrocarbon (7.0 g) was placed in the jacketed vapor feeder and pyrolyzed at 600 °C, a vaporization temperature of 140 °C, and in a nitrogen flow of 50 ml/min. Seven hours was required for the pyrolysis. The pyrolysate, an olive-green liquid, was taken up in pentane (10 ml) and chromatographed on silicic acid (300 g) with pentane as the eluting solvent. After collection of the column volume of solvent, 17-ml fractions were collected and assayed by GLC. Fractions 3–15 gave 1.60 g (23% recovery) of 1. Fractions 20–39 gave 1.90 g (27%) of 3. An analytical sample was obtained as a waxy, white solid, mp 134.0–138.6 °C (sealed capillary), by sublimation at room temperature and 0.05 mm: ν_{max} (film) 3040, 2920, 2880, 1660, 1615, and 725 cm^{-1}; UV (CH_3OH) no maximum above 200 nm, ϵ 1200 at 210 nm.

Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found (after 2 h): C, 91.23; H, 8.92; mol wt, 158 (mass spectrum), 161 (cryoscopic, benzene). Found (after 5 days): C, 85.46; H, 8.84.

As indicated by the elemental analyses, 3 is very susceptible to air oxidation, the product being a nonsublimable, friable solid which exhibits an IR spectrum very similar to that of pure 3, but with enhanced absorption at 1030, 760, and 680 cm^{-1}.

The mass spectra of 1 and 3 showed the peaks of significant intensities (%) given in Table I.

Table I

m/e	159	158	143	129	128	117	115	104	93	92	91
1	13.1	100.0	7.3	12.7	12.2	13.3	15.7	8.2	32.0	72.0	30.9
3	13.4	100.0	11.1	19.5	20.1	20.2	26.0	123	43.8	96.9	44.6
	80	79	78	77	67	66	65	51	39	27	
	31.9	*48.3*	*4.3*	*19.2*	*13.4*	*10.1*	10.5	*10.7*	21.3	12.9	
	44.5	69.2	23.8	25.2	18.9	13.2	14.2	17.1	24.3	20.0	

C. The pyrolysis tube and setup were as described for preparative pyrolysis of 1. The packing was 4–14 mesh 5% Pt/C which was shown to be active for the dehydrogenation of cyclohexane to benzene at <400 °C.

Birdcage hydrocarbon 1 (1.00 g) was vaporized from the vapor feeder at a temperature of 140 °C, and pyrolyzed at a tube temperature of 550 °C in a nitrogen flow of 176 ml/min. The pyrolysate was a feathery, white solid which in GLC exhibited the same retention time as naphthalene. Sublimation of this pyrolysate yielded naphthalene (0.10 g, 1.2%) as a white solid, mp 78.5–80.0 °C, identical with an authentic sample based on mixture melting point and infrared spectral comparison.

***all-cis*-Tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (5).** A solution of 3 (1.27 g, 8.04 mmol) in glacial acetic acid (30 ml) was hydrogenated at atmospheric pressure over 10% Pd/C catalyst (0.30 g), 16.62 mmol of hydrogen (103% of theory for 2 mol) being absorbed over a period of 140 min. The solution was filtered, diluted with water (125 ml), and extracted in succession with 50, 25, and 25 ml of pentane. The combined pentane extracts were washed with water (125 ml) and saturated aqueous sodium bicarbonate (125 ml) and dried over sodium sulfate. Filtration and evaporation of the filtrate at the water pump (room temperature) afforded 1.36 g (104%) of 5 as a white, tacky solid with an IR spectrum nearly identical with that of the analytical sample.

An analytical sample of 5 was obtained as an excessively tacky, white solid, mp 94.7–96.0 °C (sealed capillary), by recrystallization from methanol–water (ice bath) followed by sublimation at room temperature and <0.05 mm. In the IR, 5 absorbed at 2990, 2880, 1475, and 1450 cm^{-1}. The NMR spectrum of 5 exhibited unresolved multiplet absorption between δ 0.5 and 2.8.

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18; mol wt, 162.26. Found: C, 88.84; H, 11.41; mol wt, 162 (mass spectrum), 156 (cryoscopic, benzene).

***all-cis*-Tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodec-2-en-7-one (6). A.** A solid sample of 2 and its methylene chloride solution were pyrolyzed and assayed on a 3 ft × 0.25 in. o.d. copper column packed with 25% neopentyl succinate on 35–48 mesh Chromosorb P at 205 °C and 100 ml/min helium flow. The pyrolysis results are summarized in Table II.

The 5.4- and 6.9-min peaks were 2 and 8, respectively. The 8.4-min peak showed IR, NMR, and mass spectra practically identical with those of an analytical sample of 6. The half-cage ketone 11, which

Table II

Pyrolysis temp, °C	Sample	Pyrolysate composition, % 5.4 min 2	6.9 min 8	8.4 min 6	Fragmentation products
255	Solid	~0	Trace	>95	Trace
	Solution	80	Trace	20	Trace
300	Solid	~0	Trace	>95	Trace
	Solution	80	Trace	20	Trace
400	Solid	~0	Trace	>95	Trace
	Solution	20	Trace	80	Trace
500	Solid	~0	30	70	Trace
	Solution	Trace	25	75	Trace
600	Solid	~0	40	20	40
	Solution	~0	60	25	15
700	Solid	~0	~0	~0	>95
	Solution	~0	~0	~0	>95

should appear at 7.8 min, was not detected.

B. A solution of the birdcage alcohol **2** (15.0 g) in ethanol was placed in the dropping funnel and dropped through the pyrolysis tube, maintained at 500 °C, at the rate of ca. 10 drops/min in a nitrogen flow of 60 ml/min. The pyrolysate was evaporated at the water pump and the residue was taken up in benzene (100 ml) which was removed in the same way. The residue was chromatographed on silicic acid (300 g) with 5% ethyl acetate in methylene chloride as the eluting solvent. After passage of the column volume of solvent, 50-ml fractions were collected and assayed by thin layer chromatography (silica/methylene chloride). Fractions 10–23 contained the desired ketone and fractions 25–30 contained starting material. From the latter fractions there was isolated, by evaporation of solvent, 2.0 g (13% recovery) of unreacted birdcage alcohol **2** as a white solid. From the former fractions there was isolated, by evaporation of solvent, 11.9 g (79%) of ketone **6** as a pale yellow solid; their spectra were identical with those of analytical samples.

The analytical sample of **6** was obtained as a tacky, white solid, mp 182–206 °C, by crystallization from ethanol–water followed by sublimation at 80 °C and 0.02 mm: ν_{max} 3040, 2940, 1735, and 698 cm^{-1}; λ_{max} 290 nm (ϵ 15) and 212 (ϵ 900); NMR δ 5.37 (2 H, quartet, J = 5.5 Hz, olefinic), 3.24 (4 H, br s) 1.85–2.8 (8 H, m). This material proved susceptible to air oxidation, and for preservation, **6** was dissolved in ethanol directly from the chromatography column.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found (after 1 day): C, 82.10; H, 8.07; mol wt, 174 (mass spectrum). Found (after 1 week): C, 80.29; H, 7.99.

At 400 °C the pyrolysis of **2** was slight; above 550 °C the pyrolysis proceeded more completely than at 500 °C but the desired ketone **6** was contaminated with significant quantities of isomeric material, probably **9**, which could not be removed by chromatography.

***all-cis*-Tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecan-2-one (7).** A solution of ketone **6** (ca. 3.5 g, 20 mmol, directly from chromatography) in ethanol was evaporated at the water pump. The residue was then taken up in glacial acetic acid (75 ml) and was hydrogenated over 10% Pd/C analyst (0.5 g) at atmospheric pressure. Hydrogen uptake corresponded to 16.2 mmol (81% of theory for 1 mol) and ceased after 100 min. The reaction mixture was filtered and the filtrate was evaporated at the water pump to yield a white residue of **7** (3.55 g, ca. 100%) which exhibited an infrared spectrum very similar to that of an analytical sample.

The analytical sample was obtained as a tacky, white solid, mp 119.5–121.0 °C, by two crystallizations from methanol–water followed by sublimation at 80 °C and <0.05 mm: ν_{max} 2930, 2870, and 1730 cm^{-1}; λ_{max} 290 nm (ϵ 16). The NMR spectrum of **7** exhibited unresolved multiplet absorption between δ 0.8 and 3.5.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H. 9.15. Found: C, 81.83; H, 8.89.

Oxime of 6. A solution of **6** (1.74 g, 10.0 mmol, directly from chromatography) in ethanol (8.7 g of solution) was diluted with ethanol (10 ml) and water (10 ml) and to the mixture were added hydroxylamine hydrochloride (0.83 g, 12.0 mmol) and sodium acetate (1.6 g, 20 mmol). The reaction mixture was stirred at room temperature and was assayed by thin layer chromatography (silica/methylene chloride). After 18 h, when all starting material had been consumed, the reaction mixture was diluted to 200 ml with water and extracted, in succession, with 50, 25, and 25 ml of methylene chloride. The combined methylene chloride extracts were washed with two 250-ml portions of water, dried over sodium sulfate, and evaporated at the water pump to yield a white solid residue of oxime (1.72 g, 91%) which exhibited an IR spectrum identical with that of an analytical sample.

The analytical sample was obtained as white cubes, mp 159.9–161.1 °C, by two crystallizations from benzene–hexane: ν_{max} 3270, 3170, 3060, 2940, 1680, 1640, 1620, and 697 cm^{-1}; λ_{max} 225 nm (ϵ 2200). The NMR spectrum exhibited an exchangeable singlet at δ 9.2 ppm (0.8 H), an AB quartet centered at δ 5.58 (J = 5 Hz, 2.0 olefinic H), and unresolved peaks between δ 2.13 and 3.26 (12.2 H) due to the remaining protons.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.22; H, 8.15; N, 7.37.

Tosylhydrazone of 6. A mixture of **6** (6.84 g, 39 mmol, directly from chromatography) and tosylhydrazide (7.3 g, 39 mmol) in ethanol (70 ml) was stirred at room temperature for 25 h. The reaction mixture was heated to boiling, clarified with decolorizing carbon, filtered, and cooled to yield the tosylhydrazone (7.8 g, 58%) as a white solid, mp 171.8–174.0 °C, which possessed an IR spectrum identical with that of an analytical sample.

The analytical sample was obtained as white needles, mp 176.6–179.0 °C, by an additional crystallization from ethanol–water: ν_{max} 3240, 3090, 2970, 2930, 1660, 1610, 1350, and 1167 cm^{-1}; λ_{max} 274 nm (ϵ 930), 221 sh (12 400). The NMR spectrum exhibited an AB quartet centered at δ 7.84 (J = 8 Hz, aromatic) overlapping with a sharp singlet at δ 7.53 (NH, total 5.0 H), a pair of doublets (J = 6 Hz) at δ 5.34 (0.9 olefinic H) and 4.44 (0.9 olefinic H), and unresolved multiplet absorption between δ 1.9 and 3.2 (15.1 H).

Anal. Calcd for $C_{19}H_{22}N_2SO_2$: C, 66.64; H, 6.48; N, 8.18; S, 9.36. Found: C, 66.74; H, 6.44; N, 8.01; S, 9.56.

Conversion of the Tosylhydrazone to 3. A mixture of the above tosylhydrazone (6.84 g, 20 mmol), 2 N sodium hydroxide (10.0 ml), and ethanol (100 ml) was evaporated under reduced pressure. Ether (100 ml) was added to give, after filtration, 7.4 g (101%) of the sodium salt as a nonhygroscopic, white powder: ν_{max} 1230, 1140, 1125, and 817 cm^{-1}. The finely pulverized salt (1.57 g) was placed in a U tube which was directly connected to another U tube. The latter was immersed in a dry ice bath and a gentle stream of nitrogen was passed through the system while the sample was heated in an oil bath. At 140 °C the salt decomposed vigorously. The products in the dry ice trap were taken up in pentane and dried over sodium sulfate. The solvent was evaporated at room temperature under reduced pressure to yield **3** (0.18 g, 26%) as a waxy, white solid which was identical with authentic **3** by comparison of IR and NMR spectra.

Hexachloro-Birdcage Hydrocarbon 1b, 1,5,6,6,6a,7-Hexachlorodecahydro-1,5,2,4-ethanediylidenecyclopenta[*cd*]pentalene.[1a] A solution of Isodrin, 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-*endo*,*endo*-1,4:5,8-dimethanonaphthalene (197 g, Shell Chemical Co., technical) and iodine (2.0 g) in carbon tetrachloride (600 ml) was placed in a tightly stoppered, 1-l., round-bottomed Pyrex flask which was put on the roof in a position where it was exposed to direct (January) sunlight for most of the day. Solid began to appear after a few hours, but the flask was maintained in position for 5 days when thin layer chromatography (alumina, pentane) indicated the total absence of isodrin. The contents of the flask then were transferred to an evaporating dish which was placed on the steam bath under a gentle stream of nitrogen. The contents were stirred occasionally until the solvent and the bulk of the iodine had evaporated. The residue, 196 g (99.5%) of hexachloro-birdcage hy-

drocarbon, was an off-white solid, mp 295–296 °C dec, which exhibited an IR spectrum identical with that of the analytical sample, mp 299–301.5 °C dec.

Birdcage Hydrocarbon 1. A 12-l. four-necked round-bottom flask was equipped with a Hershberg stirrer, an efficient condenser with a large-bottom bore, a nitrogen inlet tube, and a thermometer. The exit from the condenser was connected through a Drierite drying tube to a bubbler containing mineral oil. The system was flushed with nitrogen and 207 g of hexachloro-birdcage hydrocarbon was dissolved in 510 g of *tert*-butyl alcohol and 3 l. of dry THF. To the stirred solution was then added 32 g of lithium ribbon (¼ × 1/16 × 2 in.) in a countercurrent of nitrogen. Within 5 min an exothermic reaction set in with evolution of hydrogen. The reaction temperature was maintained at 69–71 °C (intermittent cooling is necessary) for approximately 20 min, when the initial vigorous reaction ceased. The cooling bath was removed and the mixture was allowed to cool to 50 °C. It required about 1 h. To the mixture was then added 63 g of lithium ribbon and the reaction was again similarly controlled. When the temperature dropped to 50 °C, the mixture was refluxed on a steam bath for 1 h, cooled to 50 °C, and poured into 15 kg of ice water through a large Büchner funnel to remove the unreacted lithium ribbons. If the reaction mixture was cooled below 45 °C, it turned to a gel. The aqueous mixture was extracted with three 2-l. portions of hexane. The dried ($MgSO_4$) hexane solution was evaporated and the residual solid was sublimed at water-pump pressure on a steam bath to yield 68.5 g (76.4%) of the birdcage hydrocarbon **1**, mp 159–164 °C, ca. 92% pure. Purification by GLC gave a pure sample: mp 167–168 °C (reported mp 165–167 °C[17]); NMR (220 MHz) δ 1.40 (d, J = 10 Hz, 2 H), 1.78 (d, J = 10 Hz, 2 H), 2.28 (s, 4 H), 2.41 (s, 2 H), 2.54 (s, 4 H).

Hexachloro-Half-Cage Ketone 13. A solution of boron trifluoride etherate (4 ml) in toluene (200 ml) was placed in a 2-l. Erlenmeyer flask which was fitted with a magnetic stirrer, a thermometer, and a dropping funnel. The solution was stirred vigorously, and to it was added, from the dropping funnel, a solution of endrin, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*,*endo*-1,4:5,8-dimethanonaphthalene (Shell Chemical Co., technical, 800 g) in toluene (1500 ml), the rate of addition being adjusted so as to maintain the temperature of the reaction mixture at ca. 70 °C. At the end of the addition, two 1-ml aliquots of boron trifluoride etherate were added in succession. The first aliquot produced a significant temperature rise; the second, added after the temperature of the reaction mixture had cooled to ca. 55 °C, did not. The reaction mixture was allowed to cool to room temperature and was then filtered. The precipitate, after being washed with a little toluene and being sucked dry, amounted to 415 g (52%) of hexachloro-half-cage ketone, **13**, mp 289–291 °C (reported mp 285 °C dec).[1b]

Hexachloro-Birdcage Alcohol 14. A solution of 122.7 g of **11** in 700 ml of pyridine was refluxed for 24 h. Evaporation of the solvent followed by a recrystallization from carbon tetrachloride yielded a pyridine complex of **12**, mp 130–132 °C, resolidified at 170 °C and melted at 320 °C dec. The complex was dissolved in chloroform, washed with 2 N sulfuric acid several times, and dried ($MgSO_4$). Evaporation of the solvent gave 122.5 g of **14** as colorless crystals, mp 320 °C dec (reported mp 285 °C dec[1b]).

Birdcage Alcohol 2. Dechlorination of **14** was carried out in the manner described for the preparation of **1**, using 133 g of **14**, 520 g of *tert*-butyl alcohol, 3 l. of THF, and lithium ribbon (32 g, then 65 g). Crude products extracted with methylene chloride from two identical runs were combined and recrystallized from hexane to yield 87.7 g (72%) of **2** as colorless crystals, mp 181–192 °C, which were sublimed at water-pump pressure on a steam bath to give an analytical sample: mp 207–208 °C (reported mp 207–208 °C[1b]); NMR (220 MHz) δ 1.45 (d, J = 10 Hz, 1 H), 1.70 (s, 2 H), 1.77 (d, J = 10 Hz, 1 H), 2.12 (br s, 1 H), 2.4 (m, 5 H), 2.5 (m, 3 H), 3.90 (br s, 1 H, –OH).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.45; H, 8.05.

Methoxy-Birdcage Hydrocarbon 12a. To a solution of dimsyl sodium prepared from 3 g of 53.5% sodium hydride and 40 ml of Me_2SO was added a solution of 8.7 g of **2** in 40 ml of THF at 10 °C followed by 25 ml of methyl iodide at 20 °C. The mixture was stirred at 25 °C overnight, poured into 300 ml of ice–water, and extracted with ether twice. The combined extracts were washed with water, then saturated sodium chloride solution, dried ($MgSO_4$), and evaporated. The pale yellow, oily residue was distilled to give 9.13 g (97%) of a colorless oil, bp 86–91 °C (1.6 mm). The center cut, bp 86 °C (1.6 mm), $n^{24.5}D$ 1.5252, was analyzed: NMR δ 3.20 (s, 3 H, OCH_3), 1.65 (AB, J = 10.2 Hz, 2 H), 1.63 (s, 2 H), 2.1–2.6 (m, 9 H).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.64; H, 8.80.

Cyanate 12d. To a solution of 17.4 g of **2** in 400 ml of THF was added 60 ml of 1.7 M *n*-butyllithium in hexane at 23 °C. Gaseous cyanogen chloride was introduced through a tubing extended below the surface of the suspension at 0–3 °C. When 14 g of the reagent was added the mixture became a clear solution which was stirred at room temperature overnight. The low boilers were evaporated and the oily residue was distilled to give 13.9 g (70%) of **12d** as a colorless oil, bp 110–127 °C (0.5 mm), which solidified at room temperature. Sublimation at 60 °C gave a crystalline solid, mp 71–73 °C (sinter at 68 °C): ν_{max} (neat) 2260, 2210, 1120 cm^{-1}. The analysis of this sample indicated contamination by **2**.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.57; N, 7.03. Found: C, 78.57; H, 6.81; N, 6.11.

Distillation of **12d** at atmospheric pressure over a free flame with or without catalytic amounts of Lewis acids caused no reaction. Refluxing **12d** in toluene in the presence of boron trifluoride for 17 h followed by methanol treatment afforded a complex mixture; the desired methyl urethane could not be isolated.

***p*-Bromobenzenesulfonate 12b.** This ester was prepared from **2** and *p*-bromobenzenesulfonyl chloride in pyridine in 68% yield, mp 82–84 °C (from benzene).

Anal. Calcd for $C_{18}H_{17}SO_3Br$: C, 54.97; H, 4.63; Br, 20.30. Found: C, 54.73; H, 4.59; Br, 20.08.

***p*-Dimethylaminobenzenesulfonate 12c.** A mixture of 5.9 g of **12b** and 15 ml of dimethylamine was heated in a sealed tube at 200 °C for 24 h. The cold mixture was diluted with methylene chloride, washed successively with water and saturated sodium chloride, and dried. The solvent was evaporated and the solid residue was recrystallized from benzene–hexane to give 4.80 g (90%) of **12c** as colorless crystals, mp 116–119 °C. An analytical sample, mp 118.0–119.5 °C, was prepared by two recrystallizations from hexane: ν_{max} (Nujol) no peak above 3100, 1620 (aromatic), 1330, 1180 (sulfonate), 1350 cm^{-1} (tertiary aromatic amine).

Anal. Calcd for $C_{20}H_{23}NSO_3$: C, 67.19; H, 6.49; N, 3.92; S, 8.97. Found: C, 67.33; H, 6.58; N, 4.00; S, 9.08.

Iso-Half-Cage Ketone 8. A mixture of 10.5 g of half-cage ketone **11**[1d,18] in a potassium *tert*-butoxide solution prepared from 3.6 g of potassium and 210 ml of *tert*-butyl alcohol, was heated in a 1-l. stainless steel bomb under nitrogen at 250 °C for 4 h. The cooled mixture was poured into 250 ml of ice water and extracted with ether three times. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The slightly colored waxy residue was a ca. 96:4 mixture of **8** and **11** by GLC. A recrystallization from hexane–pentane followed by sublimation afforded 9.2 g (88%) of **8** as a colorless wax, mp 215–224 °C. An analytical sample was obtained by another recrystallization from hexane followed by sublimation at 80 °C (0.05 mm): mp 232–234 °C; ν_{max} 1733 and 1742 cm^{-1}; NMR (220 MHz) δ 1.23 (d, J = 12.5 Hz, 1 H), 1.77–2.04 (m, 5 H), 2.34–2.57 (m, 6 H), 2.61–2.80 (m, 2 H).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.74; H, 8.11.

Endo-Half-Cage Alcohol 15a. A solution of 26 g of half-cage ketone **11** in 200 ml of ether was added to a stirred suspension of 2.5 g of lithium aluminum hydride in 500 ml of ether over a 30-min period. The resulting mixture was refluxed for 1 h, cooled, and treated successively with 25 ml of water and 150 ml of 2 N sulfuric acid. The ether layer was separated, washed once with saturated sodium chloride solution, and dried ($MgSO_4$). The solvent was evaporated and the slightly colored waxy residue was sublimed at 0.15 mm on a steam bath to yield 25.2 g of crude **15a** as a colorless wax, mp 173–192 °C, which was recrystallized from hexane and resublimed. This material, mp 182–192 °C, may possibly be contaminated with its epimeric alcohol (mp 130–131 °C), and was recrystallized three times from hexane and resublimed to give an analytical sample: mp 192–194 °C; ν_{max} (CCl_4) 3636, 3343, 3083 cm^{-1} (sterically opposing C–H_{endo} stretch[1d]); NMR (220 MHz) δ 0.93 (dd, J = 12.3, 7.6 Hz), 1.36 and 1.39 (d and s, 3 H), 1.42 (d, J = 10 Hz), 2.23 (s, 1 H), 2.11 (s, 1 H), 2.13–2.41 (m, 7 H, including OH), 3.54 (dt, J = 12.3, 2.6 Hz, 1 H), 4.02 (d, J = 5 Hz, 1 H, >CHO).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.81; H, 8.97.

Oxidation of a **15a** sample, mp 174–182 °C, with chromium trioxide in pyridine afforded **11** in quantitative yield.

Reactions of Half-Cage Ketone 11 with Butyllithium. To a solution of 1.74 g of **11** in 40 ml of THF was added 6.0 ml of 1.7 M *n*-butyllithium in hexane. After the pale yellow solution was refluxed under nitrogen for 24 h, 5 ml of methanol was added and the solvents were evaporated. The residue was taken up in water and extracted with ether three times. The combined ether extracts were washed with saturated sodium chloride solution and dried ($MgSO_4$). The solvent

was evaporated to give 2.28 g of slightly colored crystals which consisted of ca. 94% **15b** and 6% **11** by GLC. Three recrystallizations from hexane followed by sublimation gave an analytical sample: mp 108–109.5 °C; ν_{max} (CCl_4) 3610 (O–H), 3086 cm^{-1} (C–H).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.95; H, 10.40.

A similar reaction of **11** with *tert*-butyllithium gave **15c** as colorless crystals: mp 84–86 °C; ν_{max} (CCl_4) 3600 (O–H), 3080 cm^{-1} (C–H).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.93; H, 10.45.

The *tert*-butyl derivative **15c** decomposed on Woelm neutral alumina (activity grade 1) and on GLC columns above 190 °C to a complex mixture of alcohols and hydrocarbons.

Iso-Half-Cage Ketoxime 8. A mixture of 34.8 g of **8**, 27.8 g of hydroxylamine hydrochloride, 25 ml of 30% sodium hydroxide solution, 45 ml of water, and 125 ml of ethanol was refluxed for 46 h, poured into 500 ml of water, and extracted three times with ether. The combined ether extracts were dried and evaporated. The colorless, crystalline residue was recrystallized from hexane to yield 34.2 g of **8**, mp 132–136 °C. An analytical sample, mp 134.5–136.0 °C, was obtained by another recrystallization from hexane followed by sublimation.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.55; H, 8.41; N, 7.33.

Registry No.—**1**, 704-02-9; **1b**, 3212-28-0; **2**, 707-05-1; **3**, 60606-96-4; **5**, 60606-97-5; **6**, 60606-98-6; **6** oxime, 60606-99-7; **6** tosylhydrazone, 60607-00-3; **6** Na salt, 60607-01-4; **7**, 60607-02-5; **8**, 707-83-5; **8** oxime, 1603-18-5; **11**, 7509-41-3; **12a**, 60607-03-6; **12b**, 741-42-4; **12c**, 60607-04-7; **12d**, 60607-05-8; **15a**, 7261-85-0; **15b**, 60607-06-9; **15c**, 60607-07-0; isodrin, 465-73-6; endrin, 72-20-8.

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(18) We obtained half-cage ketone **11** as a by-product in the triquinacene synthesis:[2] ^1H NMR (220 MHz) δ 1.32 (ddm, J = 13, 8 Hz, 1 H), 1.44 (dm, J = 10 Hz, 1 H), 1.56 (dm, J = 11 Hz, 1 H), 1.72–1.89 (m, 3 H), 2.24 (br s, 1 H), 2.30 (br s, 1 H), 2.35–2.65 (m, 6 H).

1-Cycloheptatrienylidene-4-cyclopentadienylidene-2,5-cyclohexadiene System[1,2]

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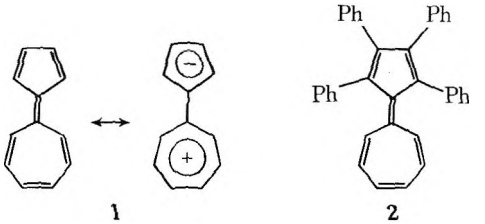
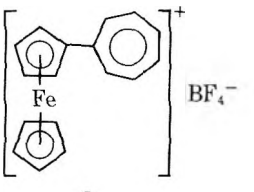
A synthesis of the parent hydrocarbon, *1-cycloheptatrienylidene-4-cyclopentadienylidene-2,5-cyclohexadiene* (**4**), was attempted. The approach was based on the dehydrogenation of the dihydro derivative **11**. Hydride abstraction of **11** did not lead to the desired tropylium salt **13**. A synthetic approach to the tetraphenyl derivative **17** involved the tropylium salt **16**. Deprotonation of **16** produced an apparent oligomer of **17**. A stable organoiron derivative **7** of **4** was prepared by a three-step synthesis starting with *p*-ferrocenylphenylmagnesium bromide (**19**).

Sesquifulvalene (**1**) is a cross-conjugated two-ring hydrocarbon of considerable theoretical interest[3] which is expected to have a certain amount of contribution to its structure from the dipolar resonance form. The parent hydrocarbon **1**[4] is unstable and could not be isolated as a solid at low temperature.[5] The tetraphenyl derivative **2** possesses the expected thermal stability.[6] The hydrocarbon **1** can also be stabilized as a ligand in transition metal complexes. This was demonstrated by the synthesis of ferrocenyltropylium fluoroborate (**3**).[7]

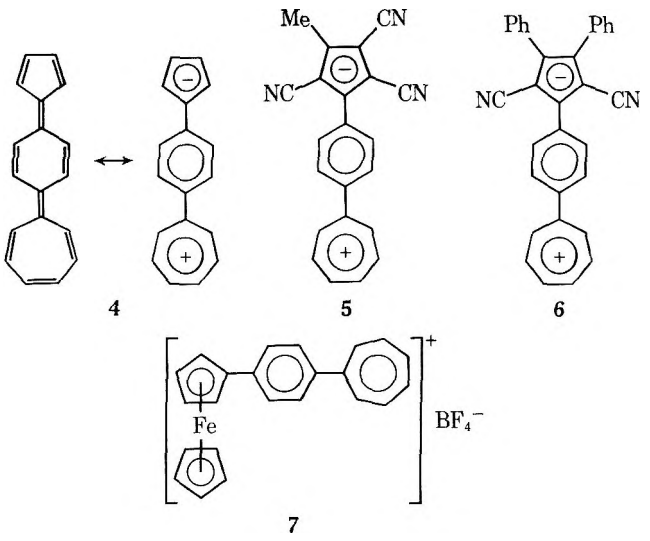


1 **2**



3

*The system **4** is a cross-conjugated three-ring hydrocarbon* having an inserted *p*-phenylene ring between the two aromatic rings of sesquifulvalene in the dipolar structure. It was of interest to study the synthesis of this long conjugated system about which very little is known. The parent hydrocarbon **4** has not yet been synthesized. Only three derivatives, **5**,[8] **6**,[9] and **7**,[2] with strong electron-withdrawing substituents or metal coordination have recently been reported. The present paper describes the preparation of the dihydro derivative **11**, which was a key intermediate in the attempted synthesis of the parent hydrocarbon **4**, and the isolation of an oligomer of tetraphenyl derivative **17**. Also included is a detailed report of the synthesis of π-cyclopentadienyliron derivative **7**.

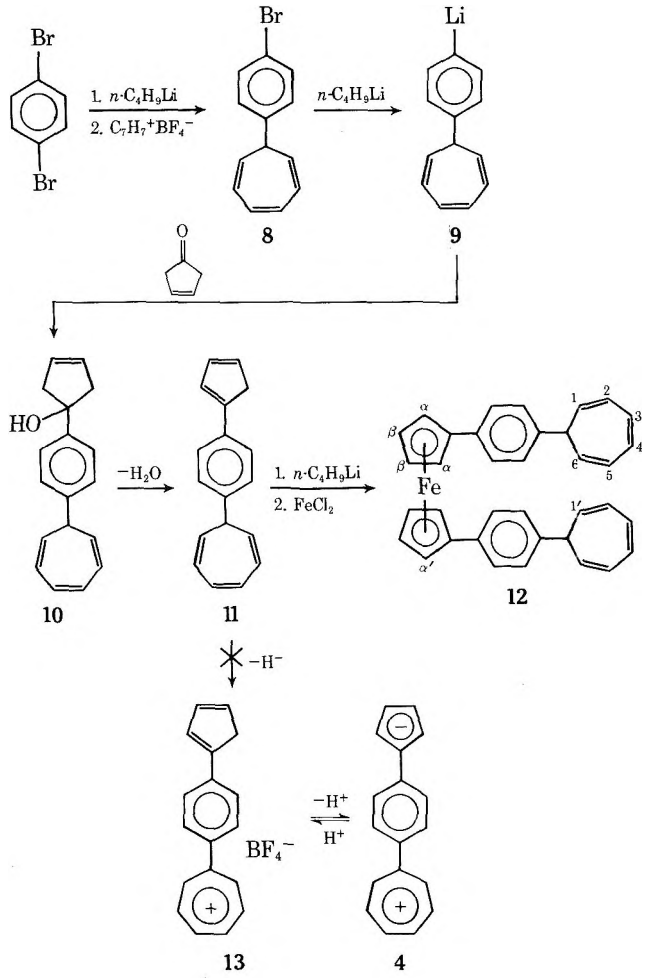


4 5 6 7

Results and Discussion

Dihydro Derivative 11 (Scheme I). The dihydro derivative 11 was synthesized from *p*-dibromobenzene by the sequence outlined in Scheme I. Thus, lithiation of *p*-dibromobenzene, followed by addition of tropylium fluoroborate, gave *p*-tropylbromobenzene (8)[10] in 56% yield. The NMR spectrum exhibited a methine proton (H_7) triplet at τ 7.34, characteristic of 7-arylcycloheptatrienes.[12,13] *p*-Tropylphenyllithium (9) was prepared via addition of *n*-butyllithium to a solution of 8, at 0 °C.[14] The lithium reagent 9 was then treated with 3-cyclopentenone at 0 °C to yield the hydroxy derivative 10 in 26% yield. The IR spectrum of carbinol 10 exhibited a hydroxy absorption peak at 3600 cm^{-1}. The NMR spectrum exhibited a multiplet at τ 7.1–7.5 for the methine and methylene protons and a broad singlet at τ 4.30 for the olefinic protons.

Scheme I

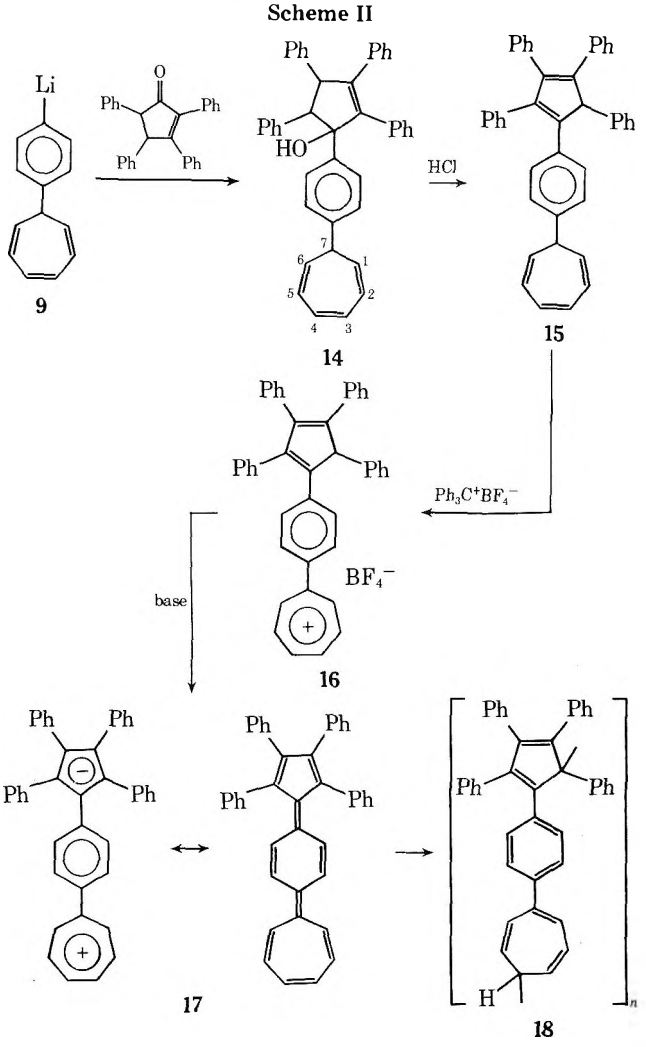


Treatment of 10 with phosphoryl chloride and pyridine at 0 °C gave the dihydro derivative 11. This compound was thermally unstable and decomposed fairly rapidly when exposed to air.[15] 1-Phenyl-1,3-cyclopentadiene also behaved similarly.[16] The mass spectrum of 11 exhibited a parent ion peak at *m/e* 232. The NMR spectrum of 11[24] showed a triplet for a methine proton (H_7) at τ 7.30 and an apparent doublet for two methylene protons (H_{11}) at τ 6.65.[17] The structure of 11 was further substantiated by treatment with *n*-butyllithium followed by ferrous chloride to give the disubstituted ferrocene derivative 12. The mass spectrum of 12 showed the expected parent peak at *m/e* 518. The NMR spectrum of 12 exhibited two triplets at τ 5.60 and 5.87, characteristic of 1,1′-diarylferrocenyl group.[19]

Treatment of 11 with triphenylmethyl fluoroborate failed to give the expected tropylium derivative 13 and afforded only intractable polymeric materials. Hydride abstraction from 11 did occur as evidenced by the isolation of triphenylmethane; however, the tropylium derivative 13 was apparently very unstable and could not be isolated. The instability of 13 could be due to the dissociation of the slightly acidic proton in cyclopentadiene to form the parent hydrocarbon 4, which was so reactive that it in turn was converted to polymeric material.[20]

Oligomer of Tetraphenyl Derivative 17 (Scheme II).

Scheme II



Addition of 2,3,4,5-tetraphenyl-2-cyclopentenone[40] to *p*-tropylphenyllithium (9) yielded the carbinol 14. The crude

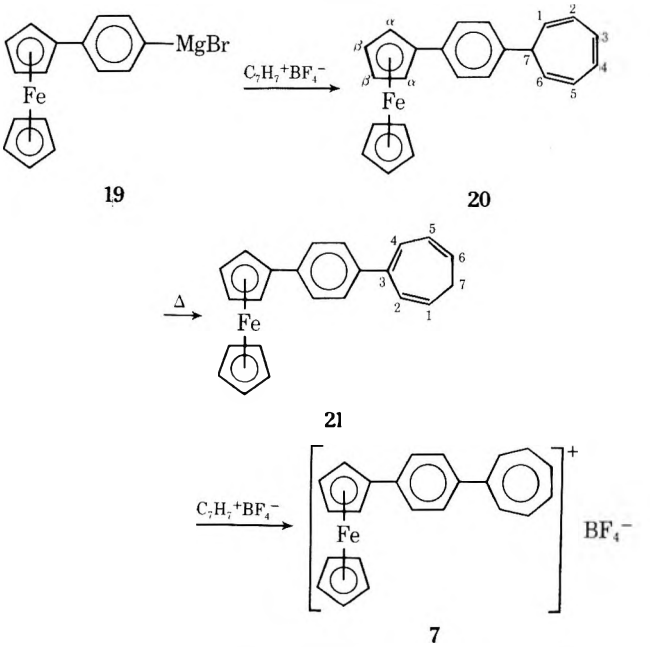
product **14** was heated at reflux with hydrochloric acid in ethanol to form the cyclopentadiene derivative **15** in 19% yield. The NMR spectrum[24] of **15** exhibited a singlet at τ 4.95 for the methine proton of the cyclopentadienyl group.[22] The mass spectrum exhibited a parent ion peak at *m/e* 536.

The tropylium salt **16** was obtained as a red solid in 83% yield by hydride abstraction of **15** with triphenylmethyl fluoroborate. This IR spectrum of **16** showed a strong absorption at 1060 cm^{-1}, indicating the presence of fluoroborate ion. The NMR spectrum exhibited a singlet for the methine proton at τ 4.31, a multiplet for the tropylium protons at τ 0.6–1.10, and a quartet for para-disubstituted aromatic ring protons at τ 2.40. The UV spectrum of **16** was markedly solvent dependent.[25] It showed λ_{max} at 355 (log ϵ 4.04) and 600 nm (3.90) in $CHCl_3$, and 377 (log ϵ 4.17) and 527 nm (4.23) in CH_3CN.

Treatment of **16** in acetonitrile with triethylamine afforded a yellow solid, mp 250 °C. A molecular weight determination by vapor pressure osmometry in benzene solution[27] indicated that the product was the dimer **18**.[28] The elemental analysis was consistent with either the monomer **17** or an oligomer **18**. The absorption spectrum of **18** exhibited no visible band as expected for an oligomer. The spectrum showed λ_{max} at 300 nm (log ϵ 4.67). The NMR spectrum exhibited broad resonances in the regions τ 3.00–5.00 (olefinic) and 7.00–7.60 (methine), indicating the presence of a substituted cycloheptatrienyl group[21,35a] as a result of polymeric linkage.[29] Presumably the tetraphenyl derivative **17** was formed as an intermediate;[30] however, its highly polar nature rendered it so reactive that it was converted to the oligomer **18**.[31]

π-Cyclopentadienyliron Derivative 7. The synthetic sequence for the preparation of **7** is outlined in Scheme III.

Scheme III



Addition of *p*-ferrocenylphenylmagnesium bromide (**19**)[32] to tropylium fluoroborate in THF gave the tropyl derivative **20** as an orange solid, mp 129–130 °C, in 25% yield. The NMR spectrum of **20** exhibited a triplet for the methine proton (H_7) at τ 7.73, a singlet at τ 6.06 for protons of the unsubstituted cyclopentadienyl group, and two triplets at τ 5.51 and 5.81 for the aryl-substituted cyclopentadienyl group.[33] The mass spectrum exhibited a parent ion peak at *m/e* 325.

In order to facilitate hydride ion removal from the tropyl ring,[12,34] the derivative **20** was isomerized to **21** in refluxing xylene. The structural assignment of **21** was based on its NMR spectrum, which exhibited a triplet at τ 7.72 for two methylene protons (H_7).

Treatment of **21** with tropylium fluoroborate in methylene chloride–acetonitrile produced the thermally stable salt **7** as a dark green solid in 50% yield. This complex did not melt below 300 °C. The ir spectrum of **7** displayed a strong absorption at 1060 cm^{-1} characteristic of fluoroborate ion. The NMR spectrum exhibited a multiplet at τ 0.7–1.31 indicating the presence of an aryl tropylium group.[35] The low-field NMR signals at τ 0.70–1.31 indicated that most of the positive charge was located on the seven-membered ring. Derivatives **5** and **6**,[8,9] having strong electron-withdrawing substituents on the five-membered ring, also displayed these characteristic low-field signals. Thus, the success of preparing a stable derivative of **4** required the presence of strong electron-withdrawing substituents or metal coordination on the five-membered ring.

Experimental Section

Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and were calibrated vs. polystyrene. NMR spectra were recorded on a Varian A-60 spectrometer or Perkin-Elmer R12A spectrometer with tetramethylsilane as internal standard. Ultraviolet spectra were obtained on a Cary 14 recording spectrometer. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMU 6L mass spectrometer by Dr. A. Siegel, University of Massachusetts.

Melting points were determined on a Mel-Temp apparatus. They are not corrected. Elemental analysis and molecular weight determinations were performed by Mr. Charles Meade of the University of Massachusetts Microanalytical Laboratory.

Ethyl ether and tetrahydrofuran were purified by drying over potassium hydroxide and sodium respectively, and were distilled from lithium aluminum hydride. Benzene was dried by azeotropic distillation. Pentane was washed with sulfuric acid and distilled from calcium hydride.

Thin layer chromatography experiments were performed with CAMAG silica gel containing ultraviolet-sensitive fluorescent indicator. Column chromatography experiments were performed with CAMAG alumina (neutral).

Commercial *n*-butyllithium in hexane solution was obtained from Alfa Inorganics, Inc. Tropylium fluoroborate,[36] 3-cyclopentenone,[37] ferrous chloride,[38] triphenylmethyl fluoroborate,[36] 3,4-diphenyl-2-cylopentenone,[39] and tetraphenyl-2-cyclopentenone[40] were prepared by published methods.

The numbering of positions in all structures is arbitrary for the convenience of proton assignments.

***p*-(7-Cycloheptatrienyl)bromobenzene (8).** *n*-Butyllithium (68 mmol) was added under nitrogen to a stirred solution of *p*-dibromobenzene (16 g, 68 mmol) in 100 ml of dry ethyl ether at 0 °C over 20 min and stirring was continued for an additional 30 min. The reaction mixture was then added under nitrogen through an addition funnel to a stirred suspension of 6.4 g (36 mmol) of tropylium fluoroborate in 100 ml of dry ethyl ether at room temperature. Following completion of the addition, the reaction mixture was allowed to stir at room temperature for 4 h. The reddish solution was then poured onto 300 ml of cold 2 N hydrochloric acid and the layers were separated. The ether layer was washed twice with 10% sodium carbonate solution and twice with sodium chloride solution, and dried (Na_2SO_4). The solvent was evaporated and the residue was extracted twice with 250 ml of hot Skellysolve B. The combined extracts were evaporated and the liquid residue was vacuum distilled (95–108 °C, 0.05 mm), affording 4.5 g (56%) of product as a pale yellow oil. The product was further purified by low temperature recrystallization from pentane. The pure product obtained was a white solid: mp 31–32 °C; bp 108–109 °C (0.05 mm) [lit.[11] bp 108 °C (0.001 mm)]; NMR ($CDCl_3$) τ 7.34 (1 H, t, H_7), 4.55–4.90 (2 H, m, $H_{1,6}$), 3.63–3.97 (2 H, m, $H_{2,5}$), 3.24–3.41 (2 H, m, $H_{3,4}$), 2.47–3.00 (4 H, m, H_{Ar}).

Anal. Calcd for $C_{13}H_{11}Br$: C, 63.18; H, 4.49; Br, 32.33. Found: C, 63.11; H, 4.34; Br, 32.30.

***p*-(7-Cycloheptatrienyl)phenyllithium (9).** To a stirred solution of **8** in ether at 0 °C was added slowly an equimolar amount of *n*-butyllithium under nitrogen. The initially colorless reaction mixture turned to yellow at the end of addition. After an additional stirring for 15 min, the reagent was ready for use.

1-*p*-(7-Cycloheptatrienyl)phenyl-3-cyclopenten-1-ol (10). A solution of *p*-tropylphenyllithium (**9**) was prepared from 5.1 g (23 mmol) of *p*-tropylbromobenzene in 60 ml of dry ethel ether and 10.5 ml (23 mmol) of *n*-butyllithium in 20 ml of dry ether. To this solution was added a solution of 1.9 g (23 mmol) of 3-cyclopentenone[37] in 25

ml of dry ether at 0 °C over a period of 15 min. Stirring was continued at this temperature for 5 h. The mixture was hydrolyzed with an aqueous solution of ammonium chloride and layers were separated. The ether layer was washed with water, dried (Na_2SO_4), and evaporated in vacuo to a yellow solid. The latter was triturated with cold Skellysolve B and recrystallized three times from ethyl ether at −78 °C to produce 1.2 g (26%) of white crystals: mp 101–102 °C; NMR ($CDCl_3$) τ 7.92 (1 H, s, H_{OH}), 7.10–7.50 (5 H, m, $H_{7,methylene}$), 4.30 (2 H, broad s, $H_{olefinic\ of\ Cp}$), 4.50–4.86 (2 H, m, $H_{1,6}$), 3.67–4.00 (2 H, m, $H_{2,5}$), 3.28–3.50 (2 H, m, $H_{3,4}$), 2.50–2.90 (4 H, m, H_{Ar}).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.24; O, 6.39. Found: C, 85.99; H, 6.92; O, 6.93.

1-*p*-(7-Cycloheptatrienyl)phenyl-1,3-cyclopentadiene (11). To a solution of the carbinol **10** (0.8 g, 3.2 mmol) in 8 ml of dry pyridine at 0 °C, 0.3 ml (3.4 mmol) of phosphoryl chloride was added by a syringe. The reaction mixture was stirred at this temperature under nitrogen for 6 h and then hydrolyzed by pouring it onto ice-cold dilute hydrochloric acid. The mixture was extracted with 150 ml of ether; the extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The brown residue was extracted twice with 15-ml portions of Skellysolve B. The extracts were evaporated under reduced pressure to produce 0.52 g (70%) of a yellow product. A purer sample was obtained by trituration with Skellysolve B at −78 °C. The product was thermally unstable, even under nitrogen at 0 °C: NMR ($CDCl_3$) τ 7.30 (1 H, t, H_7), 6.65 (2 H, d, $H_{methylene}$), 2.70–3.20 (4 H, m, H_{Ar}), 4.65–5.00 (2 H, m, $H_{1,6}$), 3.30–4.20 (7 H, $H_{2,5,3,4,olefinic\ of\ Cp}$).

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94; mol wt, 232. Found: C, 93.21; H, 5.91; mol wt. (mass spectroscopic), 232.

1,1′-Di[*p*-(7-cycloheptatrienyl)phenyl]ferrocene (12). To a stirred solution of 0.52 g (2.3 mmol) of dihydro derivative **11** in 30 ml of dry ethyl ether at 0 °C was added under nitrogen *n*-butyllithium (2.6 mmol) in 10 ml of dry ethyl ether over 10 min. Stirring at this temperature was continued for 30 min and 0.14 g (2.3 mmol) of ferrous chloride was added in one portion. The reaction mixture was then stirred at 0 °C for 2 h and at room temperature for 12 h, and hydrolyzed with 100 ml of 2 N hydrochloric acid. The mixture was extracted two times with 300-ml portions of ether; the combined ether extracts were washed twice with water and dried over Na_2SO_4. The dried ethereal solution was evaporated to dryness in vacuo and the residue was dissolved in 40 ml of benzene. The benzene solution was placed on a column of alumina. Elution with benzene gave an orange solid. The solid was crystallized from benzene to yield 0.25 g (22%) of product. An analytical sample was obtained by recrystallization from benzene: mp 163–165 °C; NMR ($CDCl_3$) τ 7.40 (2 H, t, $H_{7,7}$), 5.60 (4 H, t, $H_{\alpha\ and\ \alpha'}$), 5.87 (4 H, t, $H_{\beta\ and\ \beta'}$), 4.46–4.83 (4 H, m, $H_{1,6,1',6'}$), 3.67–4.00 (4 H, m, $H_{2,5,2',5'}$), 3.25–3.46 (4 H, m, $H_{3,4,3',4'}$), 2.64–2.95 (4 H, m, H_{Ar}).

Anal. Calcd for $C_{36}H_{30}Fe$: C, 83.40; H, 5.83; Fe, 10.77; mol wt, 518. Found: C, 83.57; H, 5.95; Fe, 10.15; mol wt (mass spectroscopic), 518.

Attempted Preparation of *p*-(1,3-Cyclopentadienyl)phenylcycloheptatrienylium Fluoroborate (13). The dihydro derivative **11** (0.2 g, 0.86 mmol) in 5 ml of methylene chloride and 0.28 g (0.86 mmol) of triphenylmethyl fluoroborate in 10 ml of methylene chloride were combined in a 25-ml flask with argon. The reaction mixture was left in a refrigerator for 2 days. After filtration, the black precipitate collected was found to be intractable material. The filtrate was evaporated to dryness; the residue was purified by column chromatography on alumina and eluted with Skellysolve B to produce 94 mg (45%) of triphenylmethane. The NMR spectrum of this compound was identical with that of an authentic sample.

1,2,3,5-Tetraphenyl-4-*p*-(7-cycloheptatrienyl)phenyl-1,3-cyclopentadiene (15). A solution of *p*-tropylphenyllithium (**9**) was prepared from 2.4 g (10.7 mmol) of *p*-tropylbromobenzene **8** in 100 ml of dry ethyl ether and 4.9 ml (10.7 mmol) of *n*-butyllithium in 30 ml of dry ether. To this solution was added a solution of 2.8 g (7.25 mmol) of 2,3,4,5-tetraphenyl-2-cyclopentenone[40] in 150 ml of benzene over 30 min at 0 °C. Stirring was continued at this temperature for 7 h. The reaction mixture was hydrolyzed with 250 ml of 2 N hydrochloric acid. The layers were separated. The organic layer was washed twice with 10% sodium carbonate solution and twice with sodium chloride solution, and dried (Na_2SO_4). The solvent was evaporated, and an IR spectrum of the residue showed an O–H stretching frequency at 3600 cm^{-1} ($CHCl_3$). The crude carbinol **14** was dissolved in 150 ml of hot ethanol. The ethanolic solution was allowed to cool to room temperature and filtered. The filtrate was then stirred at reflux under nitrogen in a 250-ml flask while 15 ml of 12 N hydrochloric acid was added dropwise through an addition funnel over 30 min. Stirring was continued under reflux for 1 h. The product gradually crystallized from the hot solution and was collected on a Buchner funnel after the solution had been cooled. Recrystallization first from chloroform–ethanol, then from ether, and again from chloroform–ethanol afforded 0.76 g (19%) of light yellow crystals: mp 180–181 °C; NMR ($CDCl_3$) τ 7.50 (1 H, t, H_7), 4.60–5.05 (2 H, m, $H_{1,6}$), 3.72–4.05 (2 H, m, $H_{2,5}$), 3.28–3.50 (2 H, m, $H_{3,4}$), 2.73–3.20 (24 H, m, H_{Ar}), 4.95 (1 H, s, $H_{methine\ of\ Cp}$); UV ($CHCl_3$) λ_{max} (log ϵ) 247 (4.46) and 347 nm (4.11).

Anal. Calcd for $C_{42}H_{32}$: C, 93.99; H, 6.01; mol wt, 536. Found: C, 94.01; H, 5.89; mol wt (mass spectroscopic), 536.

1,2,3,4,5-Pentaphenylcyclopentadiene. A solution of 0.5 g (1.3 mmol) of 2,3,4,5-tetraphenyl-2-cyclopentenone in 45 ml of benzene was added under nitrogen over 15 min to a stirred solution of phenyllithium prepared from 0.3 g (1.9 mmol) of bromobenzene and 0.86 ml (1.9 mmol) of *n*-butyllithium in 10 ml of dry ethyl ether at 0 °C. After stirring for 4 h, the reaction mixture was hydrolyzed with 2 N hydrochloric acid and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo. An IR spectrum of the residue showed an O–H stretching frequency at 3600 cm^{-1}. The crude carbinol was dissolved in 30 ml of ethanol and added to a nitrogen-flushed 100-ml flask. After the solution was heated to reflux, 30 ml of 12 N hydrochloric acid was added dropwise through an addition funnel over 30 min. Stirring was continued under reflux for 1.5 h. The product gradually crystallized from the hot solution and was collected by filtration after cooling. Four recrystallizations from benzene yield 0.19 (33%) of white crystals: mp 259–260 °C (lit.[23] 250 °C); NMR ($CDCl_3$) τ 5.00 (1 H, s, $H_{methine}$), 2.70–3.18 (25 H, m, H_{Ar}).

Anal. Calcd for $C_{35}H_{26}$: C, 94.12; H, 5.87. Found: C, 94.01; H, 5.87.

***p*-(2,3,4,5-Tetraphenyl-1,3-cyclopentadienyl)phenyltropylium Fluoroborate (16).** A mixture of 1.7 g (3.16 mmol) of the dihydro derivative **15** in 120 ml of methylene chloride, and 1.0 g (3 mmol) of triphenylmethyl fluoroborate in 30 ml of methylene chloride was left in a refrigerator for 4 days. The reaction mixture was concentrated to 30 ml via a stream of nitrogen and again left in a refrigerator overnight. Filtration gave 1.5 g (83%) of red crystals. An analytical sample was obtained by seven recrystallizations from methylene chloride, followed by drying in vacuo at 100 °C: mp 195 °C dec; NMR (acetone-d_6) τ 4.31 (1 H, s, $H_{methine}$), 2.77–3.20 (20 H, m, H_{Ar}), 2.13–2.70 (4 H, q, $H_{disub\ Ar}$), 0.60–1.10 (6 H, m, $H_{tropylium}$); IR (KBr) 1060 cm^{-1} (s, BF_4); UV ($CHCl_3$) λ_{max} (log ϵ) 355 (4.04) and 600 nm (3.90); UV (CH_3CN), λ_{max} (log ϵ) 337 (4.17) and 527 nm (4.23).

Anal. Calcd for $C_{42}H_{31}BF_4$: C, 81.04; H, 5.02; B, 1.74; F, 12.21. Found: C, 81.14; H, 5.06; B, 1.70; F, 12.12.

The filtrate from the reaction mixture was evaporated to dryness. The residue was extracted several times with hot Skellysolve B. The extracts were concentrated to a small volume and chromatographed on a column of alumina. Elution with Skellysolve B gave 0.47 g (64%) of crude triphenylmethane. Recrystallization from ethanol afforded white crystals. The NMR spectrum of this compound was identical with that of an authentic sample.

Oligomeric 1-Cycloheptatrienylidene-4-(tetraphenylcyclopentadienylidene-2,5-cyclohexadiene) (18). To a nitrogen-flushed 50-ml flask was added 1 g (1.6 mmol) of tropylium derivative **16** in 15 ml of acetonitrile. The deep red solution was cooled to 0 °C, and 0.48 g (4.8 mmol) of triethylamine in 5 ml of acetonitrile was added dropwise over 15 min. Before half of the amine was added, the deep red color of the solution was discharged. After stirring for 1 h at 0 °C, the product was collected on a Hirsch funnel. The yellow solid was transferred to an Erlenmeyer flask containing 5 ml of acetonitrile cooled at 0 °C. The suspension was stirred for 30 min and filtered. The same procedure was repeated once again to produce 0.62 g (72%) of analytically pure **18**: mp 250 °C (red liquid); bp 350 °C (decomposition with gas evolution); UV ($CHCl_3$) λ_{max} (log ϵ) 300 nm (4.67); NMR ($CDCl_3$) τ 7.00–7.60, 4.10–4.90, 3.30–3.90, 2.00–3.30.

Anal. Calcd for $C_{42}H_{30}$: C, 94.34; H, 5.66; mol wt, 534. Found: C, 94.30; H, 5.71, mol wt (osmometric in benzene), 1243.

The filtrate from the reaction mixture was evaporated and the residue was extracted with water. The aqueous extract was evaporated in vacuo to give 0.22 g (75%) of triethylammonium fluoroborate. The salt was identical with an authentic sample.

***p*-(7-Cycloheptatrienyl)phenylferrocene (20).** To a stirred suspension of 3.6 g (20 mmol) of tropylium fluoroborate in 150 ml of dry ethyl ether was added dropwise under nitrogen over 20 min a solution of *p*-ferrocenylphenylmagnesium bromide (**19**)[32] prepared from 3.4 g (10 mmol) of *p*-bromophenylferrocene, 1.1 g (10 mmol) of ethyl bromide, and 0.73 g (30 mmol) of magnesium in 100 ml of dry tetrahydrofuran. Stirring was continued for 2 h at room temperature and then for 20 min at reflux. The reaction mixture was hydrolyzed with

150 ml of 2 N hydrochloric acid. The ether layers were washed twice with 10% sodium carbonate solution and twice with water, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 5 ml of benzene, chromatographed on a 14 × 2 in. column of alumina (activity II), and eluted with Skellysolve B. The first orange band consisted of a mixture of phenylferrocene and *p*-bromophenylferrocene. The second orange band, eluted with 2:1 Skellysolve B–benzene, gave 0.75 g (21%) of product. Three recrystallizations from Skellysolve B afforded analytically pure orange crystals: mp 129–130 °C; NMR ($CDCl_3$) τ 7.73 (1 H, t, H_7), 4.50–4.82 (2 H, m, $H_{1,6}$), 3.69–4.00 (2 H, m, $H_{2,5}$), 3.26–3.48 (2 H, m, $H_{3,4}$), 6.06 (5 H, s, $H_{unsub\ Cp}$), 5.51 (2 H, t, H_α), 5.81 (2 H, t, H_β), 2.53–3.00 (4 H, m, H_{Ar}).

Anal. Calcd for $C_{23}H_{20}Fe$: C, 78.42; H, 5.72; Fe, 15.85; mol wt, 352. Found: C, 78.15; H, 5.56; Fe, 15.80; mol wt (mass spectroscopic), 352.

***p*-(3-Cycloheptatrienyl)phenylferrocene (21).** A solution of 1.0 g (2.8 mmol) of *p*-tropylphenylferrocene (**20**) in 12 ml of toluene was heated to reflux under nitrogen for 24 h. The solvent was evaporated in vacuo and the residue was recrystallized from Skellysolve B to yield 9.5 g (95%) of product: mp 123–126 °C; NMR ($CDCl_3$) τ 7.72 (2 H, t, H_7), 4.32–4.78 (2 H, m, $H_{1,6}$), 3.57–3.97 (2 H, m, $H_{2,5}$), 3.03–3.20 (1 H, d, H_4), 6.07 (5 H, s, $H_{unsub\ Cp}$), 5.80 (2 H, t, H_β), 5.54 (2 H, t, H_α), 2.70 (4 H, s, H_{Ar}).

***p*-Ferrocenylphenyltropylium Fluoroborate (7).** To a solution of 0.6 g (1.7 mol) of *p*-tropylphenylferrocene (**21**) in 20 ml of methylene chloride and 5 ml of acetonitrile was added 0.32 g (1.7 mmol) of tropylium fluoroborate in one portion. The reaction mixture was stirred at room temperature for 18 h. The final suspension was suction filtered to produce dark green crystals. The product was purified by consecutive trituration with water, ether, and benzene. The analytical sample was obtained by consecutive trituration with carbon tetrachloride, water, and ethyl ether, and dried at 110 °C for 4 days. The compound does not melt below 300 °C: IR (KBr) 1060 cm^{-1} (s, BF_4^-); NMR (CH_3CN) τ 0.70–1.30 (6 H, m, H_{1-6}), 2.10–2.30 (4 H, d, H_{Ar}), 5.10 (2 H, t, H_α), 5.45 (2 H, t, H_β), 5.90 (5 H, s, $H_{unsub\ Cp}$).

Anal. Calcd for $C_{23}H_{19}BF_4Fe$: C, 63.06; H, 4.37; Fe, 12.75. Found: C. 63.38; H. 4.62; Fe, 12.50.

Registry No.—**7,** 60595-05-3; **8,** 54615-31-5; **9,** 60582-51-6; **10,** 60582-52-7; **11,** 60582-53-8; **12,** 60595-03-1; **14,** 60582-54-9; **15,** 60582-55-0; **16,** 60582-57-2; **18,** 60582-59-4; **20,** 60595-01-9; **21,** 60595-02-0; *p*-dibromobenzene, 106-37-6; tropylium fluoroborate, 27081-10-3; 3-cyclopentenone, 14320-37-7; ferrous chloride, 7758-94-3; 2,3,4,5-tetraphenyl-2-cyclopentenone, 7317-52-4; 1,2,3,4,5-pentaphenylcyclopentadiene, 2519-10-0; triphenylmethyl fluoroborate, 341-02-6; *p*-bromophenylferrocene, 58482-65-8.

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A Ring Expansion Route to Benzo Substituted Medium- and Large-Ring Systems. Synthesis of *trans*-7,8-Benzocyclododeca-5,7-dien-1-one

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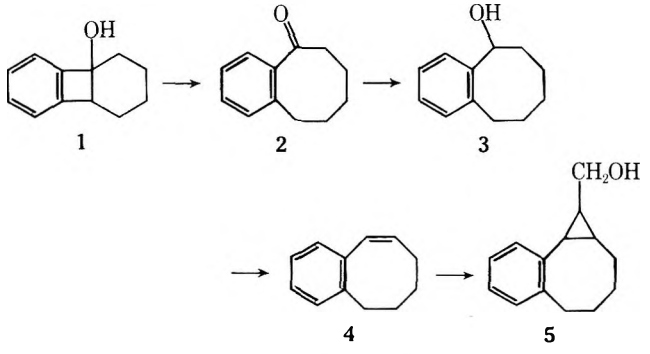
trans-7,8-Benzocyclododeca-5,7-dien-1-one (**9**) has been prepared in 11 steps from cyclohexanone using benzyne to generate 2,3-benzocyclooct-2-en-1-one which is converted to a cyclopropylcarbinyl alcohol. Acid-catalyzed rearrangement effects two-carbon ring expansion which leads to the precursor for the final siloxy-Cope two-carbon ring expansion.

The title compound has been prepared as part of an exploration of possible methods to prepare certain hormone model systems by ring expansion methods. The compound lacks some of the functionality which is ultimately desired; however, its synthesis demonstrates the feasibility of the general approach and the success of the two key ring expansions.

Results and Discussion

2,3-Benzocyclooct-2-en-1-one (**2**) was prepared via the cyclobutanol **1** by a modification of the reaction discovered by Caubere's group[1] in which the enolate of cyclohexanone is reacted with benzyne to give **1**. In our hands, the Girards reagent separation of 2-phenylcyclohexanone from **1** only gave good results if the extraction stage was done quickly under cold, neutral conditions. Otherwise the Girards adduct seemed to revert back to ketone which contaminated **1**. The rearrangement of **1** to **2** was carried out with potassium hydride in THF rather than the originally described sodium amide and HMPA which are more expensive and treacherous to work with. The overall yield is comparable to that reported.[1]

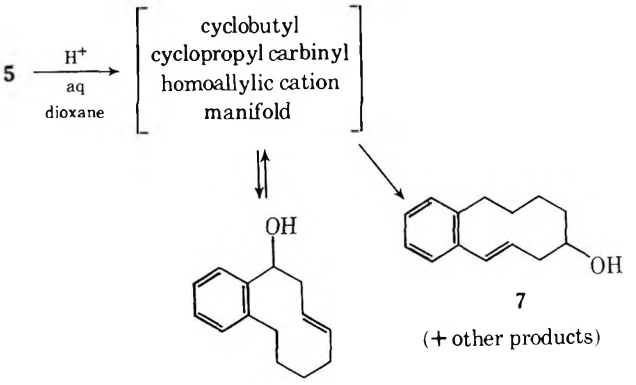
Sodium borohydride reduction smoothly gave 2,3-benzocyclooct-2-en-1-ol (**3**) which was converted to cycloalkene **4**



1 2 3 4 5

with polyphosphoric acid. This method gave the purest product of several methods tried, although some improvement may be possible since the vacuum transfer left behind a dimeric ether by-product. The addition of ethyl diazoacetate followed by lithium aluminum hydride reduction proceeded to **5** (>85% *anti*) in a straightforward manner as described earlier for the nonbenzo analog.[2] The structure of *anti*-**5** was ascertained mainly by NMR analysis including decoupling experiments that showed that the benzylic cyclopropyl proton has both cis and trans coupling constants (J = 8 and 5 Hz).

The acid-catalyzed rearrangement of bicyclo[6.1.0]nonane-9-methanol was shown earlier[2] to undergo an unprecedented rearrangement to cyclodec-3-en-1-ol. When **5** is treated under similar conditions, the rearrangement proceeds predominantly to **6**, which unfortunately is the wrong cyclodecenol for the next stage. Continued heating with increased acid concentration gives the less reactive alcohol **7** as the dominant product, but other products are also formed. Definite structure proofs were not possible on the minor components but some cyclobutanol product is clearly formed (1780-cm^{-1} band for the corresponding ketone) as well as an isomer having a cis double bond next to the benzene ring (J = 10 Hz). Most of the minor products were readily removed by dry column chromatography except for the cyclobutanol which had a similar R_f value. The structures of **6** and **7** follow readily from the spectra (see Experimental Section).



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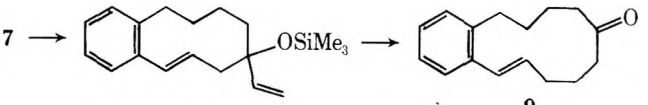
The conversion of **7** to the siloxy-Cope precursor followed the standard steps used previously[3] and the spectra confirm the expected structures. The thermolyses of **8** were similar to



8 9

earlier studies although the yields were not quite as high.[4,5] Only two-carbon ring expansion was observed which is reasonable[6] since ring contraction would lead to a more strained system and the [3,3] shift product would be higher in energy than **9**. The structure of **9** was assigned from the spectra and from decoupling experiments on the Eu(fod)$_3$ shifted NMR spectrum which demonstrated that there are three methylene groups between the carbonyl and the double bond.

A complete kinetic study was not carried out but two- and three-point rate measurements at 243.7 °C ($10^5 k = 6 \pm 1\ s^{-1}$) and at 274.1 °C ($10^4 k = 4 \pm 2\ s^{-1}$) give activation parameter estimates (E_a = 42 kcal/mol, log A = 13) which are similar to those for the nonbenzo analogue.[5]

Experimental Section

General. Spectral measurements utilized Beckman IR8, Perkin-Elmer 727B, Varian Associates HA100, and CEC 110B instruments.[7] Analytical gas–liquid chromatography (GLC) used a Varian Aerograph Model 1200 instrument with capillary or high efficiency[8] 0.125 in. columns listed: (A) 0.01 in. × 100 ft DEGS, (B) 0.125 in. × 10 ft 10% DEGS on Chromosorb W, (C) 0.125 in. × 4 ft 3% AN 600 on Chromosorb G, (D) 0.125 in. × 4 ft 7% DEGS on Chromosorb W, (E) 0.125 in. × 2.75 ft 9% OV101 on Chromosorb W.

Preparative GLC used a Varian Aerograph A90 with the columns listed: (F) 0.25 in. × 9.5 ft 3% AN 600 on Chromosorb G.

7,8-Benzobicyclo[4.2.0]oct-7-en-1-ol (1). Alcohol **1** was prepared by the method outlined by Caubere.[1] Sodium amide was prepared from 58 g (2.5 mol) of sodium.[9] The ammonia was allowed to evaporate under nitrogen and 800 ml of dry THF was added. A solution of 100 ml (1.0 mol) of cyclohexanone in 200 ml of THF was dripped in with stirring so as to maintain a temperature of 30–35 °C (about 45 min). The reaction mixture was warmed to 40 °C for 2 h and then cooled to −5 °C at which time 56 g (0.35 mol) of bromobenzene was added. The −5 °C temperature was maintained for 14.5 h (no bromobenzene left in the GLC, column A) at which time 100 ml of water was added dropwise at 0 °C. The reaction mixture was poured into 300 ml of HCl and ice and 500 ml of ether was added. The organic layer was washed with water, 5% HCl, 10% sodium bicarbonate, and saturated sodium chloride. Drying ($MgSO_4$) and solvent removal gave 124 g of crude product. A second 500-ml ether extraction of the aqueous layer gave an additional 3.7 g which was 82% cyclohexanone. GLC analysis of the 124-g portion indicated 45% cyclohexanone, 25% 2-phenylcyclohexanone, and 30% of alcohol **1**. Most of the cyclohexanone was removed by Kugelrohr distillation and then the product was transferred in the same way (100 °C air bath, 0.1 mm) which gave 36.2 g of solid (59% of **1** by GLC). The ketones were removed by heating the mixture at 80 °C for 45 min with 22g of Girard Reagent T in 350 ml of ethanol and 39 ml of acetic acid. Two-thirds of the ethanol was removed and the mixture was poured into a large beaker containing 1 l. of ether, 120 g of sodium bicarbonate, and 1 l. of ice–water. The organic layer was quickly separated in a separatory funnel and washed with bicarbonate and sodium chloride solutions. If the separation was not done quickly, near 0 °C, near neutral pH, the ketones were less completely removed. The separation gave 17 g of **1** (97% pure by GLC). Recrystallization from hexane gave pure **1**, mp 108.5–109.5 °C (lit.[1] 108–109 °C).

2,3-Benzocyclooct-2-en-1-one (2).[10] A suspension of 5.3 g of potassium hydride (Ventron) in 100 ml of hexane and 100 ml of dry THF was stirred and 5.08 g of **1** dissolved in 100 ml of dry THF was added dropwise over 45 min. The reaction mixture was stirred for an additional 1 h at room temperature and was quenched with 30 ml of water. The THF was removed and the aqueous layer was extracted with three 50-ml portions of ether which were washed with water and dried ($MgSO_4$). The 4.8 g of product was transferred by Kugelrohr (73% of **2** by GLC, column C) and then purified on a 30 by 2 in. silica dry column ($CHCl_3$) which gave 3.3 g of **2** (60% yield, one peak on GLC) which could be crystallized from petroleum ether, mp 54–55 °C (lit.[1] 56–60 °C).

2,3-Benzocyclooct-2-en-1-ol (3). Sodium borohydride reduction carried out in the same way as described for related compounds[11] gave **3** in 95% yield: IR (CCl_4) 3620, 2950, 1430, 1020, 1070, 750, 690 cm^{-1}; NMR (CCl_4) δ 1.2–2.2 (m, 9 H), 2.7 (m, 2 H), 5.1 (m, 1 H), 7.0–7.6 (m, 4 H); high-resolution mass spectrum, 176.121 (calcd for $C_{12}H_{16}O$ (M^+), 176.120).

1,2-Benzocycloocta-1,3-diene (4). A mixture of 39 g of phosphorus pentoxide and 98 ml of 85% orthophosphoric acid was warmed to 95 °C for 15 min at which time 6.8 g (0.039 mol) of **3** was added. The reaction mixture was kept at 95 °C for 35 min and then poured over ice and extracted into ether. The organic layer was washed with bicarbonate and brine and dried ($MgSO_4$). Concentration and Kugelrohr distillation give 3.73 g (61% yield) of **4** (95% pure by GLC): IR (CCl_4) 3027, 2930, 2860, 1480, 1445, 1075, 1050, 970, 770, 750, 720, 695 cm^{-1}; NMR (CCl_4) δ 2.1–2.3 (m, 2 H), 1.5–1.8 (m, 4 H), 2.8 (m, 2 H), 5.8 (d of t, J = 12 and 6 Hz, 1 H), 6.4 (d, J = 12 Hz, 1 H), and 7.1 (s, 4 H); high-resolution mass spectrum, 158.109 (calcd for $C_{12}H_{14}$ (M^+), 158.110).

2,3-Benzobicyclo[6.1.0]non-2-ene-9-methanol (5). A mixture of 75 mg of anhydrous cupric sulfate and 3.7 g (0.023 mol) of **4** was stirred under nitrogen at 70 °C as 13 ml of ethereal ethyl diazoacetate[2] (ca. 0.1 mol) was dripped in over 2 h. After 2.5 h at 75 °C the dark brown solution was filtered, concentrated, and purified by alumina chromatography to give 3.6 g of the ester: IR (CCl_4) 3200, 2970, 2400, 1700, 1430, 1360, 1300, 1150, 1175, and 1050 cm^{-1}; NMR (CCl_4) δ 0.4–0.7 (m, 1 H), 1.22 (t, J = 7 Hz, 3 H), 1.1–2.3 (m, 7 H), 2.5–3.1 (m, 3 H), 4.2 (q, J = 7 Hz, 2 H), 7.0 (s, 4 H).

A solution of 2.74 g (0.011 mol) of ester in 10 ml of ether was dripped into 2 g (0.05 mol) of $LiAlH_4$ in 40 ml of ether and stirring was continued for 16 h. The reaction mixture was quenched with 20% Rochell's salt, filtered, and dried ($MgSO_4$). Removal of solvent gave 1.92 g of **5** (54% yield from **4**, >85% anti): IR (CCl_4) 3315, 3050, 2910, 2850, 1470, 1430, and 1250 cm^{-1}; NMR (CCl_4) δ 0.7–2.2 (m, 10 H), 2.5–3.4 (m, 2 H), 3.4–3.7 (m, 2 H), 6.9 (s, 4 H); high-resolution mass spectrum, 202.135 (calcd for $C_{14}H_{18}O$ (M^+), 202.136).

Acid-Catalyzed Rearrangement of 5. A solution of 183 mg of **5**, 5 ml of *p*-dioxane, 1.2 ml of water, and 0.25 ml of 2.3 M perchloric acid was heated at 85–90 °C for 10 h, at which point 95% of **5** was gone (GLC analysis on column D, 180 °C). The reaction mixture was extracted into ether, washed with saturated $NaHCO_3$, and dried ($MgSO_4$). This gave five major components with retention times and percentages shown: 4.8 (14%), 6 (9%), 8.5 (5%), 11.2 (53%), and 13.6 (17%). The later two products were shown to be **6** and **7** (see below). When the acid concentration was doubled and heating continued for 26 h, the ratio of **6** and **7** changed from 3:1 to 1:10 [internal GLC standard experiments gave a 52% yield of **7** which was purified by dry column chromatography ($CHCl_3$ eluent) or GLC (column F, 200 °C)]. Pure **6** was shown to give mainly **7** under the same conditions.

The structure of **6** was shown to be *trans*-2,3-benzocyclodeca-2,8-dien-1-ol [IR (CCl_4) 3400, 2930, 2850, 2470, 2430, 2020, 970, 710 cm^{-1}; NMR δ 1.2–2.3 (m, 6 H), 2.4–2.8 (m, 5 H), 4.7–5.3 (m, 3 H), 6.97 (m, 3 H), 7.40 (m, 1 H)] from its spectra and those of the corresponding ketone: IR (CCl_4) 3000, 2920, 2850, 1680, 1430, 1240, 1010, 960, 720 cm^{-1}; NMR (CCl_4) δ 0.6–2.2 (m, 6 H), 2.3–2.6 (m, 2 H), 3.15 (d, J = 7 Hz, 2 H), 5.15 (d of t, J = 16, 7 Hz, 1 H), 5.33 (d of t, J = 16, 7 Hz, 1 H), 6.9–7.3 (m, 4); high-resolution mass spectrum, 200.119 (calcd for $C_{14}H_{16}O$ (M^+), 200.120).

The structure of **7** was shown to be *trans*-5,6-benzocyclodeca-3,5-dien-1-ol [IR (CCl_4) 3400, 3000, 2920, 2850, 1470, 2430, 1020, 970, 710 cm^{-1}; NMR (CCl_4) δ 1.2–2.5 (m, 7 H), 2.5–2.9 (m, 4 H), 3.77 (m, 1 H), 5.64 (m, 1 H), 6.92 (d, J = 16 Hz, 1 H), 7.32 (s, 4 H)] from its spectra and that of the corresponding ketone: IR (CCl_4) 3000, 2920, 2850, 1702, 1445, 1200, 1106, 980, 750 cm^{-1}; NMR (CCl_4) δ 1.3–2.4 (m, 4 H), 2.4–2.7 (m, 4 H), 3.15 (d, J = 8 Hz, 2 H), 5.42 (d of t, J = 16, 8 Hz, 1 H), 6.86 (d, J = 16 Hz, 1 H), 7.0–7.2 (m, 4 H); high-resolution mass spectrum, 200.119 calcd for $C_{14}H_{16}O$ (M^+), 200.120).

1-Trimethylsiloxy-1-vinyl-5,6-benzocyclodeca-3,5-diene (8). Jones oxidation[12] (54% yield) followed by reactions with vinylmagnesium bromide and Tri-Sil (70% yield) as described previously[3] gave **8**: IR (CCl_4) 3050, 3005, 2940, 2850, 1455, 1410, 1250, 1110, 1080, 1050, 980, 920, 880, 840 cm^{-1}; NMR (CCl_4) δ 0.03 (s, 9 H), 0.8–2.1 (m, 6 H), 2.37 (d, J = 7 Hz, 2 H), 2.3–2.8 (m, 2 H), 5.13 (d, J = 10 Hz, 1 H), 5.31 (d, J = 16 Hz, 1 H), 5.63 (d of t, J = 16, 7 Hz, 1 H), 6.05 (d of d, J = 10, 16 Hz, 1 H), 6.70 (d, J = 16 Hz, 1 H), 7.05 (s, 4 H); high-resolution mass spectrum, 300.194 (calcd for $C_{19}H_{28}OSi$ (M^+), 300.191).

Thermolyses of 8 were carried out at 243–293 °C in the gas phase in evacuated Pyrex ampules as described previously.[3] The product mixture was hydrolyzed[3] and analyzed by GLC (column F, 165 °C). This gave smooth conversion (52% yield by internal GLC standard) to *trans*-7,8-benzocyclododeca-5,7-dien-1-one (**9**): IR (neat) 3050, 3000, 2910, 2845, 1705, 1440, 1120, 970, 750 cm^{-1}; NMR δ 1.3–1.7 (m, 4 H), 1.7–2.1 (m, 2 H), 2.2–2.7 (m, 8 H), 5.55 (d of t, J = 16, 7 Hz, 1 H), 6.55 (d, J = 16 Hz, 1 H), 7.00 (s, 4 H); high-resolution mass spectrum, 228.153 (calcd for $C_{16}H_{20}O$ (M^+), 228.151).

Acknowledgment. This investigation was supported by NIH Research Grant 1 R01 HD 08550-01 from the National Institute of Child Health and Human Development. We thank Mrs. Susan Randall for excellent NMR assistance.

Registry No.—**2**, 829-14-1; **3**, 35448-00-1; **4**, 60676-30-4; **5**, 60676-31-5; **6**, 60676-32-6; **6** ketone, 60676-33-7; **7**, 60676-34-8; **7** ketone, 60676-35-9; **8**, 60676-36-0; **9**, 60676-37-1; ethyl 2,3-benzobicyclo[6.1.0]non-2-ene-9-carboxylate, 60676-38-2.

References and Notes

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(5) R. W. Thies and J. E. Billigmeier, *J. Am. Chem. Soc.*, **96**, 200 (1974).
(6) Only 10% of the [3,3] shift product is formed with the nonbenzo analogue. Since GLC separation is more difficult with these less volatile compounds, small amounts of [3,3] shift product or cis isomer of **9** could be missed if they were too small to see in the NMR spectrum.
(7) We thank the University of Oregon for the use of their instrument and Richard Weilesec for technical assistance.
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Organic Reactions at High Pressure. Cycloadditions with Enol and Dienol Derivatives[1]

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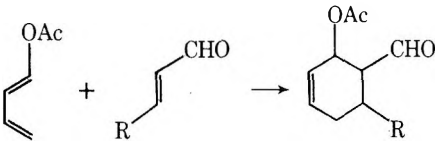
Cycloaddition reactions between 1-acetoxybutadiene and various monofunctionalized (CHO, $COCH_3$, CO_2CH_3, and CN) ethylenes (i.e., acrylic dienophiles) or propylenes (i.e., crotonic dienophiles) under the influence of 15 000 atm pressure and room temperature have been studied. With the acrylic dienophiles only the ortho-cis cycloadducts were obtained in fair to good yields; with the crotonic dienophiles only crotonaldehyde gave the desired cyclized product in 5% yield. The diminished reactivity of the crotonic dienophiles compared to their acrylic counterparts is ascribed to the combination of unfavorable steric and electronic effects brought about by the introduction of the β-methyl group. Similar results were found when 1-methoxybutadiene was employed as the diene component. No cycloaddition products were generated from ethyl vinyl ether and 1-carboalkoxybutadienes (Diels–Alder reactions with inverse electron demand) under the high pressure conditions. The utilization of high pressures (15 000–20 000 atm) and moderate temperatures (24–110 °C) provides a valuable synthetic technique in preparation of 2-alkoxy-3,4-dihydro-2*H*-pyrans from α,β-unsaturated aldehydes or ketones and vinyl ethers (heterodiene synthesis) since the high-pressure reactions can be conducted at temperatures substantially lower than those required when the reactions are carried out at atmospheric pressure. The steric and electronic effects of methyl substitution on the diene and/or dienophile are described.

The formation of a six-membered carbocyclic ring by the [4 + 2] cycloaddition process is a reaction sequence which has found extensive synthetic utilization.[3] Of the many variable parameters which could be changed to affect the success of the cycloaddition process, most attention has been directed to the study of electronic, steric, and thermal effects, and Lewis acidity catalysis. The [4 + 2] cycloaddition reaction generally possesses the interesting property of having the volume occupied by the transition state smaller than the volume occupied by the reactants, i.e., the reaction possesses a negative $\Delta V^{\ddagger}$. Indeed, this property of the cycloaddition process has led to many studies focused on the kinetic and the thermodynamic aspects of the reaction sequence as a means of gaining insight into the mechanism of the reaction sequence.[4-8] Such studies have clearly indicated that the cycloaddition reaction should proceed more readily under very high pressure since a reaction with a negative $\Delta V^{\ddagger}$ should experience an enhanced reaction rate under such conditions. Although the utility of very high pressure (8000–20 000 atm) in organic synthesis is conceptually obvious, such a parameter has not, in fact, been adequately explored.[9-11]

When reactions are performed at these very high pressures, the system does not follow the ideal rate equation since the $\Delta V^{\ddagger}$, itself, is pressure dependent. However, for cycloaddition reactions with a $-\Delta V^{\ddagger}$ of ~25 ml/mol, the rule of thumb, based upon experimental findings, is that above 1000 atm pressure (1 kbar), every kbar increase doubles the rate of the reaction.[7] Thus, the rate enhancement closely follows the general temperature dependency and indicates that a cycloaddition which occurs at 100 °C at atmospheric pressure could be achieved at 20 °C with a pressure of 9–10 kbar. The initial studies in this laboratory of the cycloaddition of heat-sensitive enamines and dienamines to electrophilic olefins at room temperature clearly demonstrated the synthetic utility of synthesis at very high pressure.[12] This study has now been extended to the cycloaddition of derivatives of enols and dienols to electron-poor unsaturated systems.

Results and Discussion

A. Cycloadditions with 1-Acetoxybutadiene. In 1947 Wichterle and Hudlicky reported that 1-acetoxybutadiene could serve as the diene component in a Diels–Alder reaction with acrolein (**1a**) to produce the cycloadduct **2a** in 50% yield after 4 h at 100 °C.[13] Similarly, the use of crotonaldehyde (**1b**) as the dienophile gave the cycloadduct **2b** in 20% yield after

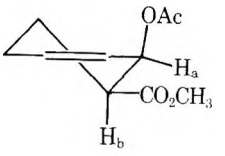


(1)

1 **2**

a, R = H
b, R = CH_3

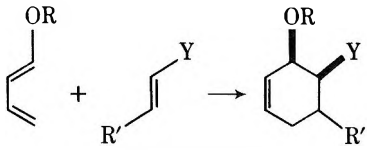
4 h at 130 °C. These transformations (eq 1) as well as some related reactions have been examined at very high pressure and the results are summarized in Table I; in no case have the reaction conditions been optimized. In each case the cycloadduct consisted of only one diastereomer based upon NMR and GC analyses. Decoupling experiments showed that the acetoxy group and the Y substituent (see Table I) were situated ortho-cis to one another, a result in complete accord with the documented[2] regioselectivity and stereospecificity of the Diels–alder reaction and consistent with the dipolar natures of the reactants. For example, it was demonstrated that upon irradiation of the olefinic protons of the cycloadduct obtained from 1-acetoxybutadiene and methyl acrylate (entry 5) proton H_a is resolved into a doublet with a coupling constant of 4 Hz; such a J value is consonant with protons H_a and H_b being in a pseudoequatorial/axial arrangement as depicted in formula **3**.[14]



3

As can be seen from the data in Table I, the employment of very high pressure in the reaction of acrolein with 1-acetoxybutadiene offers a significant improvement in the yield of the cycloadduct **1a** as compared to the thermally promoted reaction. In the case of crotonaldehyde, however, the high-pressure procedure gave cycloadduct **2a** in a significantly lower yield than did the thermal reaction; considerable polymerization of the reactants attended the high-pressure experiment (entry 2). Likewise, substantial amounts of polymer were produced when methyl acrylate or acrylonitrile (entries 5 and 7, respectively) served as dienophiles. With the exception of crotonaldehyde (entry 2), none of the crotonic dieno-

Table I. Products from Cycloadditions with 1-Acetoxybutadiene[a]



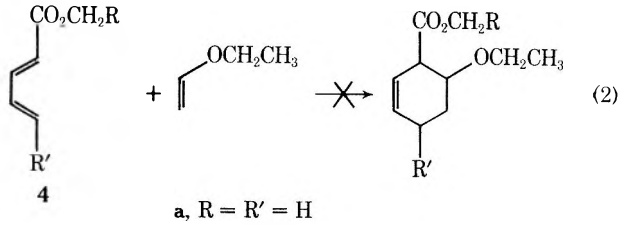
Registry no.	Entry	R	R′	Y	Time, h	Yield,[b,c] %
	1	CH_3CO	H	CHO	4	81[d]
	2	CH_3CO	CH_3	CHO	11	5[e]
	3	CH_3CO	H	$COCH_3$	4	45[d]
	4	CH_3CO	CH_3	$COCH_3$	11	0[e]
60581-96-6	5	CH_3CO	H	CO_2CH_3	4	19[e]
	6	CH_3CO	CH_3	CO_2CH_3	4	0[e]
60581-97-7	7	CH_3CO	H	CN	4	5[d]
	8	CH_3CO	CH_3	CN	12	0[e]
	9	CH_3	H	CHO	4	47[d]
60581-98-8	10	CH_3	CH_3	CHO	4	30[e]
	11	CH_3	CH_3	CO_2CH_3	12	0[d]

[a] All reactions were conducted at 15 000 atm pressure and room temperature for the times indicated. [b] Yields refer to isolated, purified materials. [c] All products displayed NMR, IR, and MS data consistent with the assigned structures. All new compounds gave satisfactory combustion analyses. [d] Unreacted starting material. [e] Unreacted starting material and polymer.

philes (entries 4, 6, and 8) gave any monomeric products. The diminished reactivity of the crotonic dienophiles compared to their acrylic counterparts very likely reflects a retardation of the rate of cycloaddition as a consequence of the combination of unfavorable steric and electronic effects imparted by the β-methyl group.

In addition to the cycloadditions of 1-acetoxybutadiene (entries 1–8), a few cycloaddition reactions with 1-methoxybutadiene (entries 9–11) were investigated. Again, a single diastereomeric cycloadduct was produced from each reaction (entries 9 and 10), and homonuclear decoupling experiments showed that the methoxy and formyl groups were disposed in an ortho-cis arrangement. The thermally induced reactions have been reported to take place in yields of 62% (100 °C, 3 h) with acrolein and 55% (150 °C, 6 h) with crotonaldehyde,[15] which are somewhat better than the high pressure promoted reactions.

B. Cycloadditions with 1-Carboalkoxybutadienes. The cycloadditions assembled in Table I are examples of Diels–Alder reactions with normal electron demand. Diene syntheses with *inverse electron demand*[3] have also been studied in which the diene component has an electron-withdrawing carbonyl group attached to a terminus and the dienophile is an enol ether (eq 2). In no case was the desired cycloadduct



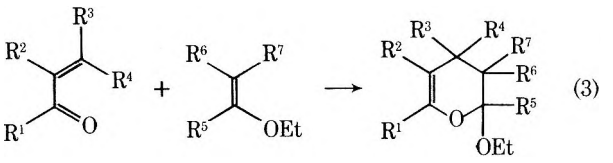
(2)

4

a, R = R′ = H
b, R = R′ = CH_3
c, R = H; R′ = CO_2CH_3

produced in detectable amount. Thus, at 15 kbar and 25 °C, 1-carbomethoxybutadiene (**4a**) and ethyl vinyl ether gave only polymeric material. Only starting materials were recovered when ethyl sorbate (**4b**) and ethyl vinyl ether were allowed to react at 15 kbar and room temperature, while when the reactions were carried out under more forcing conditions (15 kbar and 87 °C or 40 kbar[16] and room temperature) only polymeric material was produced. Subjecting the doubly activated diene dimethyl muconate (**4c**) and ethyl vinyl ether to 15 kbar pressure and 25 °C resulted in no reaction. The results of the present study may be contrasted with those reported previously for enamines in which generally high yields (greater than 80%) of cycloadducts are obtained from the very high pressure induced inverse Diels–Alder reactions.[12]

C. Heterodiene Synthesis with Vinyl Ethers. In 1950 Longley and Emerson described the thermally promoted cycloadditions of enol ethers and α,β-unsaturated aldehydes and ketones (eq 3).[17] The dihydropyran adducts have proved to



(3)

be useful synthetic intermediates[18] and research on this cycloaddition process remains active.[19] A systematic investigation on the utilization of high pressure for the heterodiene synthesis has been undertaken and the results are collected in Table II. Inspection of the data in Table II reveals several interesting features. For the reactions involving acrolein and enol ethers (entries 12–14) respectable yields of cycloadducts were obtained from the high-pressure experiments compared to the purely thermal reactions. As anticipated, increasing the number of β-methyl groups on the dienophile from zero (entry 12) to two (entry 14) brought about successive, moderate reductions in the yields of dihydropyran formation, probably reflecting the retardation of the rate of reaction as a consequence of steric hindrance in the transition state. The fact that more drastic reductions in yields were not observed is ascribable to the enhancement of the dienophilicity by the electron-donating inductive effects of the methyl groups which tend to counteract the unfavorable steric effects.

For the reactions of crotonaldehyde with various enol ethers (entries 17–19) external heating was required to render the yields of cycloadduct production satisfactory. Thus, when crotonaldehyde and ethyl vinyl ether were subjected to 15 kbar pressure for 19 h at room temperature only about a 30% yield of the desired dihydropyran was produced; unreacted starting materials made up the remainder of the material balance. When the reaction was conducted at 15 kbar pressure and 75 °C, the cycloadduct was obtained in 89% yield. Crotonaldehyde and ethyl propenyl ether failed to react when subjected to 15 kbar pressure at room temperature, but did provide a 35% yield of cycloadduct when the reaction was carried out at 15 kbar pressure and 100 °C (entry 18). For the

Table II. Products from the Heterodiene Synthesis

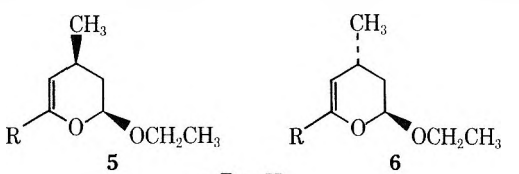
								High pressure reaction data				Thermal reaction data			
Entry	R^1	R^2	R^3	R^4	R^5	R^6	R^7	P, kbar	t, h	T,[a] °C	%[b]	t, h	T, °C	%[b]	Ref
12	H	H	H	H	H	H	H	15	20	RT	69	12	140	84	17a
13[d]	H	H	H	H	H	H	CH_3	15	23	RT	53[e]			28	*f*
14	H	H	H	H	H	CH_3	CH_3	15	20	RT	44	3	180	54	*g*
15	H	H	H	H	CH_3	H	H	15	19	RT	23	16	130	50	17a
16	H	CH_3	H	H	H	H	H	15	20	RT	0	21	150	40	17a
17	H	H	CH_3	H	H	H	H	15	24	75	89	15	175	87	17a
18[d,k]	H	H	CH_3	H	H	H	CH_3	15	20	100	35[h]				
19	H	H	CH_3	H	H	CH_3	CH_3	15	20	100	0				
20	H	H	C_6H_5	H	H	H	H	15	24	75	95	12	180	60	17a
21	CH_3	H	H	H	H	H	H	15	20	RT	62	16	140	50	17a
22[l]	CH_3	H	CH_3	H	H	H	H	15	20	110	68				
23	CH_3	H	CH_3	CH_3	H	H	H	20	18	110	50	18	200	0	*h*
24	H	H	H	H	OC_2H_5	H	H	15	2	RT	39	14	125	70	*i*
25	H	H	CH_3	H	OC_2H_5	H	H	15	2	RT	9				
26	CH_3	H	H	H	OC_2H_5	H	H	15	2	RT	0	16	125	24	*i*

[a] RT stands for room temperature, nominally about 24 °C. [b] Yields refer to isolated, purified materials. All products displayed NMR, IR, and MS data consistent with assigned structures; all new products gave satisfactory combustion analyses. [d] The ethyl propenyl ether used consisted of a 68:32 mixture of the cis (R^7 = CH_3) and trans (R^6 = CH_3) isomers. [e] Product consisted of a 61:39 mixture of cis and trans cycloadducts; see Experimental Section. [f] G. Descotes, J.-C. Martin, and N. Mathicolonis, *Bull. Soc. Chim. Fr.*, 1077 (1972). [g] K. C. Brannock, *J. Org. Chem.*, 25, 258 (1960). [h] Product consisted of an inseparable mixture of diastereomers. [i] This work. [j] V. M. Thuy, *Bull. Soc. Chim. Fr.*, 4429 (1970). [k] Registry no., 322-32-7. [l] Registry no., 60581-99-9.

reaction of crotonaldede and ethyl isobutenyl ether (entry 19) no cycloadduct was produced even after 20 h at 15 kbar pressure and 100 °C. The diminished reactivity of crotonaldehyde compared to the corresponding reactions with acrolein is attributable to the β-methyl group which introduces steric hindrance in the transition state and also renders the diene less electron poor as a consequence of induction.

Additional insight on the effects of alkyl substitution on the diene component was gained by studying the reactions of a series of α,β-unsaturated ketones with ethyl vinyl ether (entries 21–23). With methyl vinyl ketone the dihydropyran cycloadduct was obtained in 62% yield after 20 h at 15 kbar pressure and room temperature. With pent-3-en-2-one and ethyl vinyl ether no reaction took place at 15 kbar pressure and room temperature, but at 15 kbar pressure and 110 °C, a 68% yield of the cycloadduct was obtained. With mesityl oxide (which bears two β-methyl groups) and ethyl vinyl ether only a trace of the desired product was generated (according to NMR analysis) after 20 h at 15 kbar pressure and 110 °C, but by increasing the pressure to 20 kbar and maintaining the temperature at 110 °C a 50% yield of the dihydropyran was achieved. When this latter reaction was conducted in a normal sealed tube at 200 °C only unreacted starting materials and a small amount of polymer were recovered. Thus, the combination of very high pressure and moderate temperatures is extremely effective in overcoming the combined adverse steric and electronic effects which can occur in the heterodiene cycloaddition process.

For the reactions involving crotonaldehyde or pent-3-en-2-one with ethyl vinyl ether (entries 17 and 22, respectively) two stereoisomeric cycloadducts are possible, depending upon whether the 4-methyl group and the ethoxy group are cis (**5**)

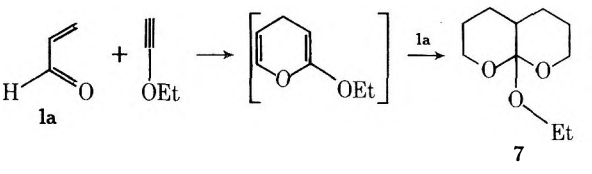


5 **6**

a, R = H
b, R = CH_3

or trans (**6**) to one another. In the high-pressure experiment with *trans*-crotonaldehyde, a single dihydropyran cycloadduct was produced whose NMR spectrum is identical with that of authentic *cis*-2-ethoxy-4-methyl-3,4-dihydro-2*H*-pyran (**5a**).[20] Likewise, *trans*-pent-3-en-2-one reacted in a highly stereoselective manner to afford a 10:1 mixture of diastereomers (as determined by GC analysis). Previous results have demonstrated that the cis isomer (i.e., **5a** or **5b**) predominates in heterodiene syntheses involving β-substituted α,β-unsaturated aldehydes or ketones and β-unsubstituted vinyl ethers.[21]

Several other miscellaneous heterodiene synthesis reactions have been investigated at high pressure. Substitution of vinyl acetate for ethyl vinyl ether and isopropenyl acetate for ethyl isopropenyl ether in reactions with acrolein led only to polymeric materials after subjection to 15 kbar pressure. Similarly, 1-ethoxycyclopentene or dihydropyran and acrolein gave mostly polymeric material in addition to some unconsumed reactants.[22] Employment of 1,1-diethoxyethylene was expected to produce substantial improvements in the yields of dihydropyran adducts compared to those attained with ethyl vinyl ether. However, polymerization of the reactants was the predominant reaction course, and relative to the thermally promoted reactions[23] the yields of cycloadducts from the high-pressure reactions (entries 24–26) are low. Likewise, utilizing 1-ethoxyacetylene as the dienophile in the heterodiene synthesis was not very successful owing to extensive polymer formation; only with acrolein was any cycloadduct obtained, which consisted entirely of the bis adduct **7** (eq 4).



1a **7** (4)

Conclusion

The utilization of very high pressures (15 000–20 000 atm) as a technique in organic synthesis has been a valuable parameter. While the results presented here for the [4 + 2] cycloadditions involving enol and dienol derivatives have not been as highly successful as those reported by us previously for the Diels–Alder reactions of enamines and dienamines[12]

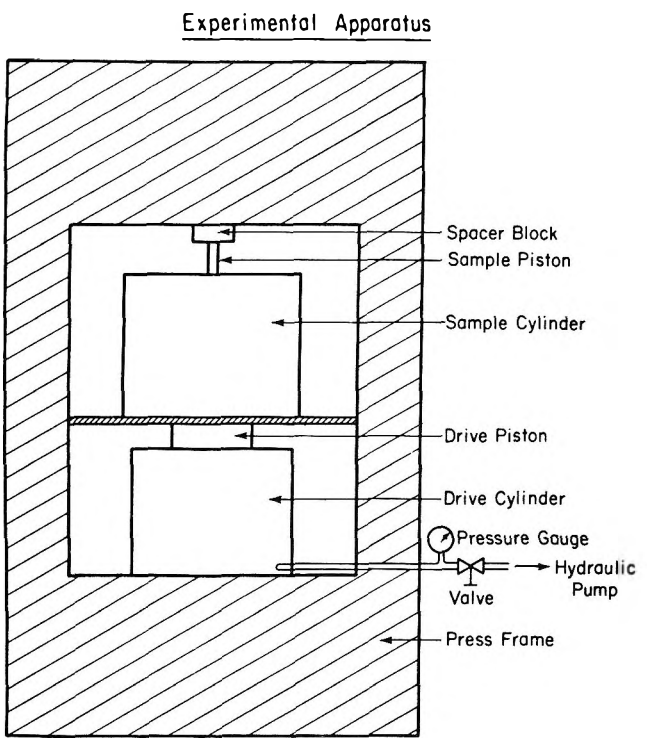


Figure 1. Schematic representation of apparatus for high-pressure experiments.

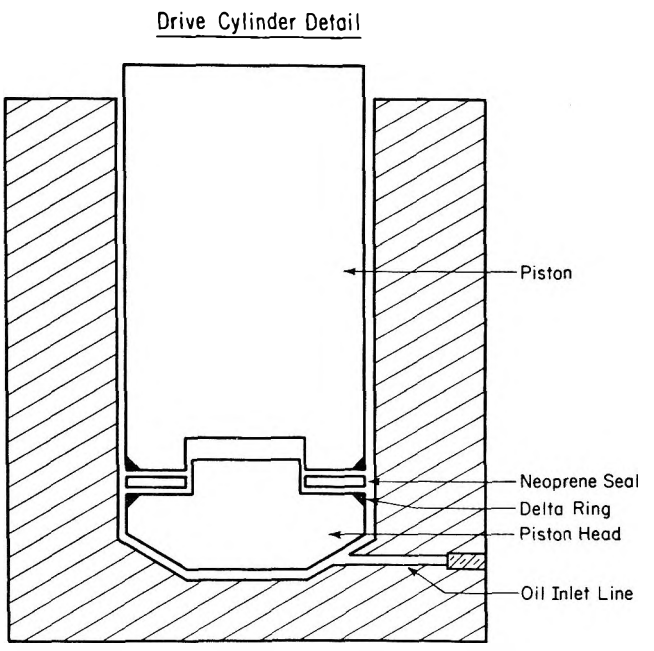


Figure 2. Detailed schematic version of the drive cylinder component of the high-pressure apparatus.

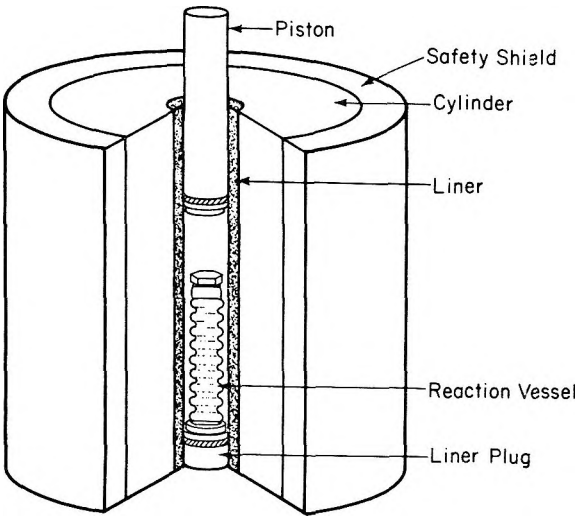


Figure 3. Detailed sketch of the sample cylinder system for high-pressure experiments.

or furans,[24] the high-pressure procedure does provide the important advantage of being able to carry out reactions at temperatures substantially lower than those required at atmospheric pressure.

Experimental Section

Apparatus.[25] Figure 1 presents a schematic version of the equipment used in our high-pressure studies. The apparatus consists essentially of a press frame, a drive cylinder, and a sample cylinder. The press frame was made from 8-in. thick hot rolled plate steel; its exterior dimensions are 5 ft long by 3 ft wide, and the cavity for the drive and sample cylinders measures 3 ft long by 2 ft wide. The drive cylinder (fabricated from hardened S-5 tool steel) is shown diagrammatically in Figure 2. The cylinder body is 13 in. long by 12 in. diameter, and the piston assembly has a diameter of 6 in. The two-stage arrangement of the piston and piston head provides for a Bridgeman unsupported-area seal. The sample cylinder system (also made from S-5 tool steel) consists of a cylinder body which measures 8 in. o.d. by 2 in. i.d. by 8 in. long, and a hardened 2 in. o.d. by 0.75 in. i.d. liner which is press-fitted into the bore of the cylinder body; a 0.5 in. thick wall aluminum tube is employed as a safety shield around the cylinder body (Figure 3). The bottom of the liner bore is stoppered by means of a stationary plug, which like the moveable piston at the top is equipped with a combination O-ring and delta ring sealing assembly to prevent leakage of the pressure transmitting fluid (kerosene) during pressurization. The reaction vessel is merely an annularly bellowed copper tube with a nut and bolt assembly at the top to contain the sample.

Carrying out a high-pressure reaction is simple. The sample tube is filled completely with the reactants and an appropriate solvent, sealed with a lead washer, and immersed in the kerosene-filled bore of the cylinder. The sample piston is seated at the top of the bore, and then forced into the bore by raising the sample cylinder by means of a hydraulic pump until the desired applied pressure is attained. To conduct a reaction at elevated temperature the sample cylinder system is first heated to the desired temperature with a tubular heating mantel. At the conclusion of the high-pressure experiment the pressure is relieved and the reaction processed in the usual fashion.

Materials. 1-Acetoxybutadiene,[26] 1-methoxybutadiene,[27] 1-carbomethoxybutadiene,[28] dimethyl muconate,[29] ethyl propenyl ether,[30] ethyl isobutenyl ether,[31] ethyl isopropenyl ether,[32] and 1,1-diethoxyethylene[33] were prepared and purified according to literature procedures; other reagents were available from commercial sources.

General. Boiling points are uncorrected. Infrared spectra were obtained as neat films with a Perkin-Elmer 137 or 710A spectrometer. Nuclear magnetic resonance spectra were recorded as solutions in carbon tetrachloride with internal Me_4Si on a Varian Associates T-60 or Hitachi Perkin-Elmer R24B spectrometer. Gas chromatographic analyses and collections were performed on a Hewlett-Packard 5700A instrument utilizing a 10 ft by 0.25 in. diameter stainless steel column packed with 10% SE-30 on Chromosorb W. Mass spectra were measured at 70 eV on a MS-12 instrument. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley. Representative high-pressure experiments are detailed below. Complete spectral data for all new monomeric products obtained in the present investigation appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.

***cis*-1-Acetoxy-2-acetylcyclohex-5-ene.** A solution of 1-acetoxybutadiene (1.30 g, 11.6 mmol) and methyl vinyl ketone (0.86 g, 12.3 mmol) in diethyl ether (approximately 10 ml) was subjected to 15 000 atm hydrostatic pressure for 4 h at 24 °C, after which the reaction mixture was filtered to remove a small amount of white, sticky material plus starting material. The filtrate was concentrated on a rotary evaporator to give 1.62 g of a clear, slightly yellow liquid which was distilled (bp 76–79 °C, 0.30 Torr) to provide 0.94 g (45%) of the pure cycloadduct as a clear, colorless liquid: NMR δ 5.5–6.3 (m, 3,

olefinic and CHOCOCH$_3$), 2.4–2.8 (m, 1, CHCOCH$_3$), 1.7–2.4 (m, 4, CH$_2$CH$_2$), 2.10 (s, 3, CHOCOCH$_3$), 1.93 (s, 3, CHCOCH$_3$); IR 3040, 1730, 1710, 1240 cm^{-1}; MS *m/e* (rel intensity) 122 (52, M − CH$_3$CO$_2$H), 107 (44, M − CH$_3$CO$_2$H − CH$_3$), 78 (100).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.19; H, 7.81.

***cis*-1-Methoxy-2-formylcyclohex-5-ene.** A solution of 1-methoxybutadiene (0.42 g, 5 mmol) and acrolein (0.5 ml, 7.5 mmol) in diethyl ether (10 ml) was held at 15 000 atm pressure for 4 h at room temperature, after which the reaction mixture was concentrated to afford 0.73 g of a clear, colorless liquid which was distilled (bp 45–46 °C, 0.40 Torr) to provide 0.33 g (47%) of the pure cycloadduct as a colorless oil: NMR δ 9.65 (s, 1, CHO), 5.8–6.2 (m, 2, olefinic), 4.1 (m, 1, CHOCH$_3$), 3.36 (s, 3, OCH$_3$), 1.6–2.6 (m, 5, CHCH$_2$CH$_2$); IR 3030, 2820, 2720, 1720, 1085 cm^{-1}; MS *m/e* (rel intensity) 108 (36, M − CH$_3$OH), 84 (45), 79 (100).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.53.

***cis*- and *trans*-2-Ethoxy-3-methyl-3,4-dihydro-2*H*-pyrans.** Ethyl propenyl ether (2.90 g, 33.7 mmol) as a 68:32 mixture of cis and trans isomers and acrolein (1.86 g, 33.2 mmol) in diethyl ether (40 ml) were allowed to react under the influence of 15 000 atm hydrostatic pressure for 23 h at room temperature, after which the solution was concentrated to a clear, colorless liquid (2.50 g, 53%) which contained a trace amount of starting material. Pure material consisting of a 61:39 mixture of **7** and **8** according to GC analysis was obtained by distillation (bp 44–45 °C, 13.5 Torr).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.28; H, 9.68.

Pure samples of the cis and trans isomers were obtained by preparative GC. Cis adduct: NMR δ 6.07 (d of t, *J* = 6, 1 Hz, 1, =CHO), 4.89 (d, *J* = 1 Hz, 1, O–CH–O), 4.6 (m, 1, CH=CH–O), 3.62 (m, 2, OCH$_3$), 1.83 (m, 3, CH$_2$CH), 1.35 (t, *J* = 7 Hz, 3, CH$_2$CH$_3$), 0.95 (d, *J* = 6 Hz, 3, CHCH$_3$); IR 3020, 1645, 730 cm^{-1}; MS *m/e* (rel intensity) 142 (M$^+$, 18), 97 (15), 86 (82), 58 (100), 57 (35). Trans adduct: NMR δ 6.08 (d of t, *J* = 6, 1 Hz, 1, C=CHO), 4.6 (m, 1, CH=CH–O), 4.50 (d, *J* = 4 Hz, 1, OCHOCH$_2$), 3.64 (m, 2, OCH$_2$), 1.3–2.6 (m, 3, CH$_2$CH), 1.20 (t, *J* = 6 Hz, 3, CH$_2$CH$_3$), 0.96 (d, *J* = 7 Hz, 3, CHCH$_3$); IR 3025, 1650, 732 cm^{-1}; MS *m/e* (rel intensity) 142 (M$^+$, 15), 97 (12), 86 (75), 58 (100), 57 (36).

***cis*-2-Ethoxy-4-methyl-3,4-dihydro-2*H*-pyran (5a).** Crotonaldehyde (3.50 g, 50 mmol) and ethyl vinyl ether (10 ml, 100 mmol) dissolved in diethyl ether (total volume approximately 50 ml) were subjected to 15 kbar pressure at 75 °C for 20 h, after which the solvent and unreacted starting materials were removed on a rotary evaporator providing 6.30 g (89%) of **5a** as a clear, colorless liquid whose NMR and IR spectra and gas chromatogram revealed the product to be pure: NMR δ 6.10 (d of d, *J* = 6, 2 Hz, 1, =CHO), 4.79 (d of d, *J* = 8, 2 Hz, 1, O–CH–O), 4.5 (m, 1, CH=CH–O), 3.60 (m, 2, OCH$_2$), 1.4–2.6 (m, 3, CHCH$_2$), 1.17 (t, *J* = 7 Hz, 3, CH$_2$CH$_3$), 1.01 (d, *J* = 7 Hz, 3, CHCH$_3$); IR 3025, 1639, 740 cm^{-1}; MS *m/e* (rel intensity) 142 (M$^+$, 12), 99 (13), 97 (19), 96 (24), 72 (82), 44 (100).

2-Ethoxy-4,4,6-trimethyl-3,4-dihydro-2*H*-pyran. A solution of mesityl oxide (2.50 g, 25.5 mmol) and ethyl vinyl ether (5.0 ml, 50 mmol) in approximately 20 ml of ethyl ether was subjected to 20 000 atm pressure for 18 h at 110 °C. The solution was concentrated to a clear, colorless liquid whose NMR spectrum indicated that the material consisted of the dihydropyran cycloadduct and mesityl oxide in a ratio of about 1:1. By distillation 2.12 g (50%) of pure product was obtained as a clear, water-white liquid: bp 69–70 °C (14 Torr); NMR δ 4.78 (t, *J* = 5 Hz, 1, OCHOCH$_2$CH$_3$), 4.20 (s, 1, =CH), 3.60 (m, 2, OCH$_2$CH$_3$), 1.67 (s, 3, =CCH$_3$), 1.54 (d, *J* = 5 Hz, 2, CHCH$_2$), 1.16 (t, *J* = 7 Hz, 3, OCH$_2$CH$_3$), 1.03 (s, 3, CCH$_3$), 0.98 (s, 3, CCH$_3$); IR 3020, 1660, 787 cm^{-1}; MS *m/e* (rel intensity) 170 (M$^+$, 17), 155 (21), 125 (12), 109 (17), 85 (16), 83 (28), 81 (11), 73 (11), 72 (100), 44 (58), 43 (97).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.28; H, 10.46.

2,2-Diethoxy-4-methyl-3,4-dihydro-2*H*-pyran. An ethereal solution of crotonaldehyde (0.86 g, 12.3 mmol) and 1,1-diethoxyethylene (1.42 g, 13.6 mmol) and a few milligrams of hydroquinone was held at 15 kbar pressure for 4 h at room temperature, after which the reaction mixture was filtered to remove a substantial amount of intractible material and the filtrate concentrated and distilled (bp 40 °C, 0.2 Torr) to provide 0.216 g (9%) of pure product as a clear, colorless liquid: NMR δ 6.09 (d of d, *J* = 7, 2.5 Hz, 1, =CHO), 4.52 (d of t, *J* = 7, 2.5 Hz, 1, CHCH=CH), 3.54 (q, *J* = 7 Hz, 4, OCH$_2$ and OCH$_2$), 1.3–2.8 (m, 3, CHCH$_2$), 1.19 (t, *J* = 6 Hz, 3 H, OCH$_2$CH$_3$), 1.14 (t, *J* = 6 Hz, 3, OCH$_2$CH$_3$), 1.00 (d, *J* = 8 Hz, 3, CHCH$_3$); IR 3050, 1645, 735 cm^{-1}; MS *m/e* (rel intensity) 186 (M$^+$, 12), 141 (57), 116 (51), 113 (89), 97 (29), 89 (44), 87 (22), 71 (47), 69 (40), 61 (31), 55 (27), 45 (35), 43 (100).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 63.90; H, 9.53.

1-Ethoxy-2,10-dioxabicyclo[4.4.0]deca-3,8-diene (7). Acrolein (1.68 g, 28.4 mmol) and ethoxyacetylene (0.8 g, 11.4 mmol) in ethyl ether (total volume 8 ml) was subjected to 15 kbar for 8 h at room temperature, after which the reaction mixture was filtered to remove quite a bit of white polymeric material and the filtrate concentrated to 0.558 g of viscous, yellow liquid whose NMR spectrum indicated it to be mostly polymer. Preparative GC provided samples of **7** as the only volatile product for spectra: NMR δ 6.02 (d of t, *J* = 6, 1.5 Hz, 2, C=CH–O), 4.6 (m, 2, CH=CH–O), 3.74 (q, *J* = 7 Hz, 2, OCH$_2$CH$_3$), 2.3–1.6 (m, 5, CH$_2$CHCH$_2$), 1.14 (t, *J* = 7 Hz, 3, OCH$_2$CH$_3$); IR 3020, 1650, 733 cm^{-1}; MS *m/e* (rel intensity) 182 (M$^+$, 5), 154 (30), 137 (27), 126 (54), 125 (48), 108 (16), 98 (93), 97 (100), 81 (19), 80 (14), 79 (16) 70 (32), 69 (21), 68 (12), 57 (12), 55 (30), 53 (18), 43 (13), 42 (28), 41 (47).

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Registry No.—**5a**, 17322-76-8; **7**, 60581-95-5; *cis*-1-acetoxy-2-acetylcyclohex-5-ene, 60582-00-5; 1-acetoxybutadiene, 1515-76-0; methyl vinyl ketone, 78-94-4; *cis*-1-methoxy-2-formylcyclohex-5-ene, 60582-01-6; 1-methoxybutadiene, 3036-66-6; acrolein, 107-02-8; *cis*-2-ethoxy-3-methyl-3,4-dihydro-2*H*-pyran, 60582-02-7; *trans*-2-ethoxy-3-methyl-3,4-dihydro-2*H*-pyran, 60582-03-8; *cis*-ethyl propenyl ether, 4696-25-7; *trans*-ethyl propenyl ether, 4696-26-8; ethyl vinyl ether, 109-92-2; 2-ethoxy-4,4,6-trimethyl-3,4-dihydro-2*H*-pyran, 60582-04-9; mesityl oxide, 141-79-7; 2,2-diethoxy-4-methyl-3,4-dihydro-2*H*-pyran, 60582-05-0; 1,1-diethoxyethylene 2678-54-8; ethoxyacetylene, 927-80-0.

Supplementary Material Available. NMR and IR spectral data for all new compounds reported here but not described in the Experimental Section (entries 5, 7, 10, 18, and 22), and complete details for the fabrication of the high-pressure apparatus (13 pages). Ordering information is given on any current masthead page.

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Syntheses of the Optically Active Multilayered [2.2]Paracyclophanes with Known Absolute Configurations[1]

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Starting from (*R*)-(−)-4-methyl[2.2]paracyclophane, a series of optically active, multilayered [2.2]paracyclophanes (**10, 11, 14,** and **15**) with known absolute configurations were synthesized; the "chiral recognition" principle was applied for the preparation of (*R,R,R*)-(−)-five-layered [2.2]paracyclophane (**14**). The chiroptical properties of these compounds are described.

Interesting features about the multilayered [2.2]paracyclophanes with benzene rings closely packed together by means of a *p*-ethano bridge are the distortion of the benzene rings and the transannular interaction caused by the closely spaced face-to-face arrangement of the aromatic rings. Recently, racemic modifications of such multilayered compounds were synthesized and their unusual physical and chemical properties were reported.[2]

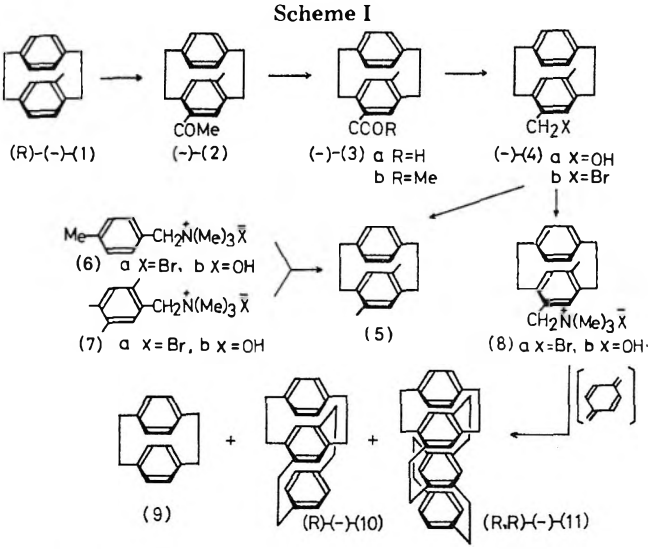
In an earlier paper,[3] we reported the preparation of [8][8]- and [8][10]paracyclophanes which have two para bridges spanning the benzene ring giving rise to D_2 and C_2 symmetry, respectively. Upon building up multilayered [2.2]paracyclophanes by Longone's method[2a,b] we also encounter molecules with C_2 or D_2 symmetry, because steric hindrance should cause the formation of molecules with these symmetries to be more favorable. We have been interested in the preparation of these "gyrochiral"[4] compounds with C_2 or D_2 symmetry as well as the chiroptical properties inherent to their helical structures. This contribution is concerned with the synthesis of a series of optically active, multilayered [2.2]paracyclophanes with known absolute configurations.

Results and Discussion

(*R*)-(−)-[3]Chochin (10) and (*R,R*)-(−)-[4]Chochin (11).[5] Our general scheme for the preparation of optically active multilayered [2.2]paracyclophanes can be seen in Scheme I, which illustrates the synthetic route to the two- and three-layered [2.2]paracyclophanes, **10** and **11**.

(*R*)-(−)-4-Methyl[2.2]paracyclophane (**1**),[6] whose absolute configuration had been determined, served as our starting material as well as a liaison compound relating the stereochemistry of the [2.2]paracyclophane series to that of our multilayered compounds. Acetylation of **1** with acetyl chloride

Scheme I



and anhydrous aluminum chloride afforded the acetyl derivative **2**, which was further converted by a haloform reaction into (*R*)-(−)-carboxylic acid (**3a**), mp 205–206 °C, $[\alpha]^{21}D$ −224°. The methyl ester **3b** of this acid was reduced with lithium aluminum hydride to the alcohol **4a** which was converted into the quaternary ammonium bromide **8a**, mp 213–215 °C, $[\alpha]^{20}D$ −94°, via the bromide **4b**. Since the bromide **4b** is a crucial compound for the following transformations, we established its structure before continuation of our synthesis. Upon lithium aluminum hydride reduction, the bromide **4b** gave a (−)-4,7-dimethyl derivative (**5**), the structure of which was confirmed by the independent synthesis of its racemic modification involving the "cross cou-

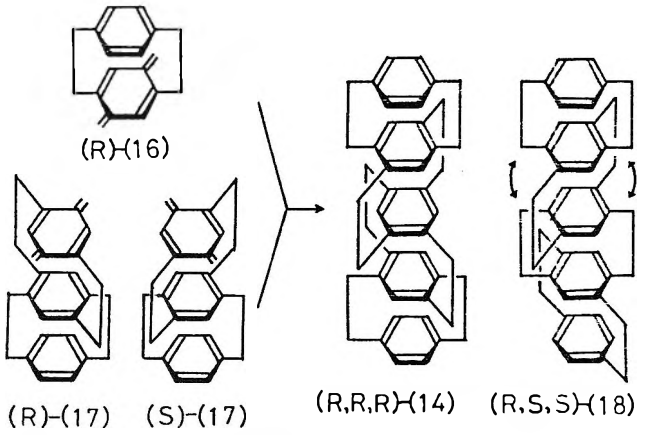
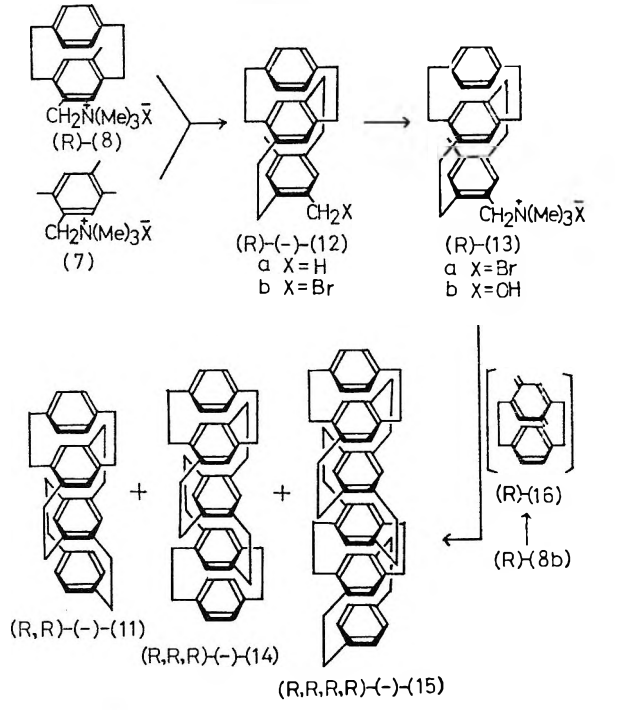


Figure 1. Chirality growth of [*n*]chochin.

pling"[7] between the two Hofmann bases, **6b** and **7b**, derived from *p*-xylene and durene, respectively. Thus having prepared intermediate **4b** with known structure, we could proceed with our synthetic sequence. A mixture of (*R*)-(−) quaternary salt (**8a**) and *p*-xylyltrimethylammonium bromide (**6a**) (1:1) was treated with silver oxide to furnish a mixture of the Hofmann bases which was then pyrolyzed in boiling toluene. Evolution of trimethylamine occurred smoothly, and the resulting reaction mixture was fractionated by chromatography on neutral alumina to give [2.2]paracyclophane (**9**, 7%), (*R*)-(−)-triple-layered [2.2]paracyclophane (**10**, 5%), mp 170–171 °C, and (*R,R*)-(−)-quadruple-layered compound (**11**, 4%), mp 230–231 °C.

(*R,R,R*)-(−)-[5]Chochin (14) and (*R,R,R,R*)-(−)-[6]-Chochin (15). As the key intermediate for the synthesis of optically active six-layered [2.2]paracyclophane, we selected (−)-triple-layered [2.2]paracyclophane (**12**) (Scheme II) which

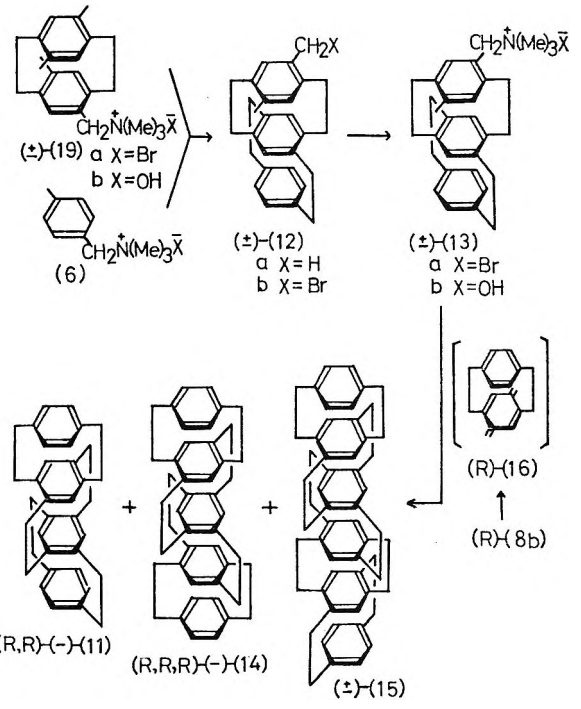
Scheme II



possesses C_2 symmetry and which could be prepared by cross-coupling between previously mentioned (*R*)-(−)-**8** and 2,4,5-trimethylbenzyltrimethylammonium base (**7**). Monobromination with *N*-bromosuccinimide followed by quaternization with trimethylamine converted the dimethyl derivative **12a** into (−)-ammonium bromide **13a** which was again cross-coupled with (*R*)-(−)-**8a**. The reaction mixture, after chromatography, afforded the following sequence of components: (*R,R*)-(−)-quadruple-layered [2.2]paracyclophane (**11**, 6%), (*R,R,R*)-(−)-five-layered compound (**14**, 3%), mp >300 °C, and (*R,R,R,R*)-(−)-six-layered compound (**15**, 1.4%), mp >300 °C.

Preparation of (*R,R,R*)-(−)-[5]Chochin (14) by the Chiral Recognition Principle. So far our guiding principle for constructing optically active multilayered [2.2]paracyclophanes has been such that an optically active intermediate with known absolute configuration was dimerized or coupled with an achiral precursor such as **7b**. We now divert attention from the above approach to a second one which involves the coupling of the optically active two-layered intermediate **16** with the racemic triple-layered intermediate **17** (Figure 1). A priori two diastereomers, **14** and **18**, could be expected; however, inspection of a molecular model indicates that the one (**18**) with *R,S,S* configuration has an "eclipsed" interaction between two ethano bridges as indicated by the curved arrows in Figure 1. This would make diastereomer **18** less stable than diastereomer **14** with helical D_2 symmetry, explaining the predominance of **14** in the product mixture. The synthetic scheme for this "chirality recognition" approach is shown in Scheme III. The (±)-triple-layered dimethyl[2.2]paracyclo-

Scheme III



phane (**12a**) prepared from the (±)-double-layered Hofmann base (**19b**) and **6b**, was treated with *N*-bromosuccinimide to furnish the (±)-monobromide **12b** which in turn was converted into the (±)-triple-layered quaternary ammonium salt (**13a**) according to Longone's procedure.[2a,b] Cross-breeding pyrolysis of a mixture of this racemic Hofmann base **13b** and the optically active double-layered Hofmann's base (*R*)-**8b** afforded, as was expected, (*R,R,R*)-(−)-five-layered [2.2]-paracyclophane (**14**, 3%), mp >300 °C, $[\alpha]^{22}D$ −362°, as the cross-coupling product, and (*R,R*)-(−)-quadruple-layered [2.2]paracyclophane (**11**, 7%) as the product of self coupling of the optically active two-layered starting material. Since isolation of the (*R,R,R*)-five-layered compound (**14**) meant that the double-layered xylylene derivative (*R*)-(**16**) from the optically active intermediate (*R*)-(**8b**) coupled preferentially with (*R*)-(**17**) over its enantiomer (*S*)-(**17**), there must be left behind a mixture of (*R*)-(**17**) and (*S*)-(**17**) slightly rich in the

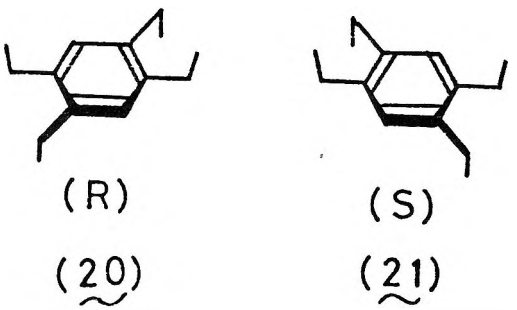


Figure 2. Planar chirality of the inner benzene rings in [*n*]chochin.

Table I. Number of Stereoisomers of [*n*]Chochin

n	*N*	D_2 isomer	C_{2h} isomer	C_2 isomer
3	2	2		
4	3	2	1	
5	6	4		2
6	10	4	2	4
7	20	8		12
8	36	8	4	24

latter. We anticipated the isolation of (*S,S,S,S*)-(+)-six-layered paracyclophane from the reaction mixture, but so far we have been unable to isolate this optically active six-layered compound, the only isolable six-layered compound being the racemic modification (**15**, 0.5%).

Nomenclature. Having succeeded in the preparation of optically active multilayered [2.2]paracyclophanes, it seems pertinent to discuss their nomenclature in which special emphasis is placed upon designation of stereochemistry. Vögtle's nomenclature[8] considerably simplifies the cumbersome IUPAC names; e.g., the quadruple-layered [2.2]paracyclophane (**11**) would be named as [2.2](1,4)(1,4)[2.2](2,5)(1,4)-[2.2](2,5)(1,4)cyclophane. In spite of its logical approach, the names derived from this system are still long and especially inconvenient for describing stereochemistry. To remedy these difficulties, we would like to propose a genetic name "[*n*]-chochin"[9] for the family of multilayered compounds constructed solely from [2.2]paracyclophane units, where *n* represents the number of layers. Furthermore, the stereochemistry of an [*n*]chochin may be expressed by specifying the planar chirality[10] of each of the inner benzene rings. Figures 1 and 2 illustrate the application of this nomenclature. The symmetry inherent to an [*n*]chochin permits us to derive the following formula which will give the total number (*N*) of stereoisomers, where *n* is the number of layers. Since the repeating element is a [2.2]paracyclophane, whole stereoisomers have at least C_2 symmetry; when *n* is odd, the stereoisomers of [*n*]chochin are all chiral belonging to either D_2 or C_2 point groups; when *n* is even, there can arise achiral meso compounds which have C_{2h} symmetry. Table I tabulates the number of the stereoisomers for successive members (n = 3–8) of [*n*]chochin calculated by means of the formulas below.

n odd ($n \geq 3$)	*n* even ($n \geq 4$)
$N = 2^{n-3} + 2^{(n-3)/2}$	$N = 2^{n-3} + 2^{(n-4)/2}$
D_2 isomers: $2^{(n-1)/2}$	D_2 isomers: $2^{(n-2)/2}$
C_2 isomers: $2^{n-3} - 2^{(n-3)/2}$	C_2 isomers: $2^{n-3} - 2^{(n-2)/2}$
	C_{2h} isomers: $2^{(n-4)/2}$ (meso)

Chiroptical Properties. Figure 3 records the circular dichroism curves in isooctane of (*R*)-(−)-4,7-dimethyl[2.2]-paracyclophane (**5**), (*R*)-(−)-**10**, (*R,R*)-(−)-**11**, (*R,R,R*)-(−)-**14**, and (*R,R,R,R*)-(−)-**15**. A common stereochemical feature among these compounds is the presence of the benzene ring(s)

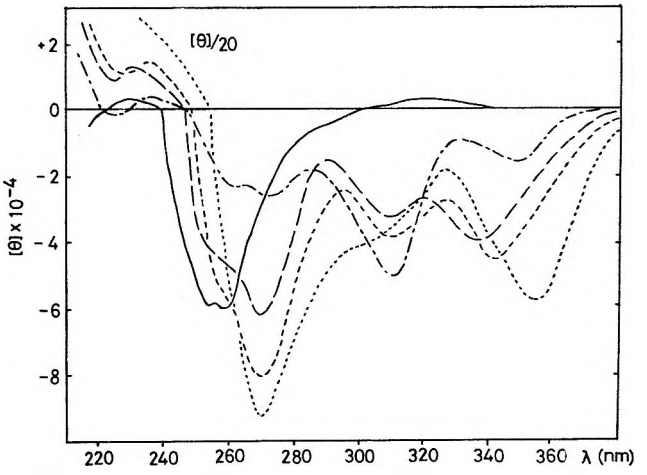


Figure 3. CD spectra of (*R*)-(−)-(**5**) (—), (*R*)-(−)-(**10**) (— — —), (*R,R*)-(−)-(**11**) (– –), (*R,R,R*)-(−)-(**14**) (- - - -), and (*R,R,R,R*)-(−)-(**15**) (· · ·) in isooctane.

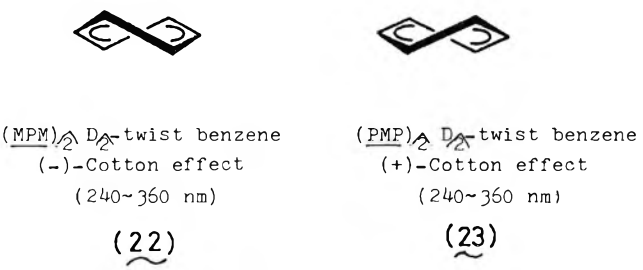


Figure 4. Chirality of D_2-twist benzene.

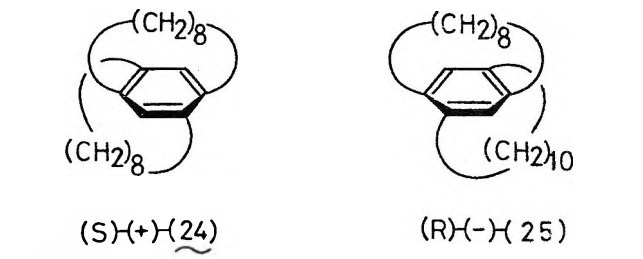


Figure 5.

with the *R* planar chirality (**20**). As has been established by x-ray diffraction,[10] these benzene rings are not planar but instead distorted, having puckered conformations with approximate D_2 symmetry.

The Cahn–Ingold–Prelog nomenclature[11] for conformational chirality can be extended to specify the chiralities of the enantiomeric D_2-twist benzenes as shown in Figure 4: $(MPM)_2$ D_2-twist benzene (**22**) and $(PMP)_2$ D_2-twist benzene (**23**). Inspection of molecular models indicates that the benzene rings in [2.2]paracyclophanes with the *R* planar chirality (**20**) suffer a distortion corresponding to the $(MPM)_2$ D_2-twist benzene ring (**22**), whereas the ones with the *S* planar chirality are deformed to have the $(PMP)_2$ D_2-twist benzene ring (**23**). The CD spectra (Figure 3) reveal that the compounds with $(MPM)_2$ D_2-twist benzene ring (**22**) exhibit negative Cotton effects at 240–360 nm. This generalization is supported by the positive Cotton effect observed in (*S*)-(+)-[8][8]paracyclophane (**24**) [with $(PMP)_2$ conformation] and negative Cotton effect observed in (*R*)-(−)-[8][10]paracyclophane (**25**) [with $(MPM)_2$ conformation].[12] In contrast to the rather simple CD spectra of these [*m*][*n*]paracyclophanes, the CD spectra of the multilayered [2.2]paracyclophanes are more complex, exhibiting bands which can be grouped roughly into 270, 310, and 340–360 nm regions. Face-to-face interactions between the distorted benzene rings should be responsible for this fine

structure.[13] Theoretical analyses of the CD spectra of the multilayered [2.2]paracyclophanes as well as of [m][n]paracyclophanes are in progress in our laboratory.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectral data were obtained from a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained from a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Hitachi EPS-3T spectrometer. Circular dichroism data were measured on a JASCO J-20 spectropolarimeter with CD attachment. Mass spectral data were measured on a Hitachi RMS-4 spectrometer.

(*R*)-(−)-4-Acetyl-7-methyl[2.2]paracyclophane (2). To a solution of anhydrous aluminum chloride (46 g) and acetyl chloride (32 g) in 1,1,2,2-tetrachloroethane (500 ml) at −30 °C was added in one portion (−)-4-methyl[2.2]paracyclophane (**1**,[6] 45 g). The mixture was kept at −15 to −20 °C with stirring for 10 min, and was then poured over ice. The separated organic phase was washed with 2 N hydrochloric acid, water, 3% sodium bicarbonate solution, and again with water, and then dried. After evaporation of the solvent, the solid product was recrystallized from methanol to give **2** (43 g, 81%): mp 142–143 °C; $[\alpha]^{22}D$ −127° (*c* 0.34, $CHCl_3$); IR (KBr) 1670 (C=O), 1587, 1536, 1496, 1430, 1353, 1264, 948, 908, 876, 802, 723 cm^{-1}; NMR ($CDCl_3$) τ 3.16–3.95 (m, 6 H), 5.85–6.25 (m, 1 H), 6.52–7.55 (m, 7 H), 7.60 (s, 3 H), 7.92 (s, 3 H).

Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.31; H, 7.65.

(*R*)-(−)-4-Carbomethoxy-7-methyl[2.2]paracyclophane (3b). Bromine (60 g) was added during 30 min to a stirred solution of potassium hydroxide (60 g) in water (250 ml) at 0 °C. A solution of (−)-**2** (30 g) in dioxane (500 ml) was added to the hypobromite solution during a period of 1 h with continued cooling and stirring. The mixture was then stirred for 3 h at room temperature. The excess oxidizing reagent was destroyed by adding a solution of sodium bisulfite (2 g) in water (250 ml). After acidification of the solution with dilute hydrochloric acid, the precipitate was collected and dried under vacuum. The resulting crude acid was recrystallized from methanol to yield **3a** (24 g, 80%), mp 205–206 °C, $[\alpha]^{21}D$ −224° (*c* 0.52, $CHCl_3$).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.08; H, 6.81.

This acid **3a** was esterified by heating under reflux for 2 h with methanol (200 ml) containing concentated sulfuric acid (10 ml). The cooled solution was then poured into water, and the product was extracted with ether. The ether extracts were washed with water, 3% sodium bicarbonate solution, and again with water, and then dried. After removal of the ether, the product was recrystallized from methanol to give **3b** (22 g, 87%): mp 136–137 °C; $[\alpha]^{22}D$ −192° (*c* 0.34, $CHCl_3$); IR (KBr) 1670 (C=O), 1590, 1546, 1497, 1436, 1411, 1276, 943, 919, 876, 799, 717 cm^{-1}; NMR ($CDCl_3$) τ 0.2 (broad s, 1 H), 3.12–3.88 (m, 6 H), 5.59–6.06 (m, 1 H), 6.50–7.57 (m, 7 H), 7.88 (s, 3 H).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.34; H, 7.22.

(*R*)-(−)-4-Hydroxymethyl-7-methyl[2.2]paracyclophane (4a). A solution of **3b** (41 g) in dry tetrahydrofuran (300 ml) was added dropwise to a suspension of lithium aluminum hydride (5.5 g) in dry tetrahydrofuran (200 ml). The mixture was heated under reflux for 6 h, and excess reducing reagent was decomposed by addition of ethyl acetate. After the mixture was acidified with dilute hydrochloric acid, the organic phase was extracted with ether. The ether solution was washed with water, 3% sodium bicarbonate solution, and again with water, and then dried. After evaporation of the ether, the solid material was recrystallized from benzene–hexane to give **4a** (32 g, 91%): mp 100–101 °C; $[\alpha]^{23}D$ −133° (*c* 0.39, $CHCl_3$); IR (KBr) 3400 (O–H), 1590, 1495, 1450, 1435, 1407, 1064, 1026, 993, 910, 873, 800, 716 cm^{-1}; NMR ($CDCl_3$) τ 3.22–3.78 (m, 6 H), 5.36–5.71 (AB quartet, J_{AB} = 12.8 Hz, 2 H), 6.45–7.50 (m, 8 H), 7.93 (s, 3 H), 8.33 (s, 1 H).

Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.87; H, 8.03.

(*R*)-(−)-4-Bromomethyl-7-methyl[2.2]paracyclophane (4b). To a stirred solution of the alcohol **4a** (73 g) in dry ether (2 l.) was added dropwise a solution of phosphorus tribromide (78.3 g) in dry ether (400 ml) at room temperature. The mixture was stirred for 2 h at room temperature, and water (300 ml) was slowly added to the reaction mixture. The separated organic phase was washed with dilute sodium bicarbonate solution and water, and then dried. After removal of the ether, the solid product was recrystallized from carbon tetrachloride to yield **4b** (78 g, 87%): mp 138–139 °C; $[\alpha]^{22}D$ −23° (*c* 0.76, $CHCl_3$); IR (KRr) 1590, 1495, 1456, 1433, 1409, 1372, 1214, 946, 912, 878, 807, 767, 729, 717 cm^{-1}; NMR ($CDCl_3$) τ 2.97–3.96 (m, 6 H), 5.53–5.83 (AB quartet, J_{AB} = 10.4 Hz, 2 H), 6.42–7.94 (m, 8 H), 7.91 (s, 3 H).

Anal. Calcd for $C_{18}H_{19}Br$: C, 68.57; H, 6.09. Found: C, 68.76; H, 5.98.

(*R*)-(−)-4,7-Dimethyl[2.2]paracyclophane (5). A solution of **4b** (0.5 g) in dry tetrahydrofuran (7 ml) was added dropwise to a suspension of lithium aluminum hydride (0.2 g) in dry tetrahydrofuran (10 ml). The mixture was heated under reflux for 10 h, and the excess reducing reagent was decomposed by addition of dilute hydrochloric acid. The aqueous and organic layers were separated and the aqueous layer extracted with ether. The combined organic layers were washed with 3% sodium bicarbonate solution and water and dried. After concentration, the solid material was recrystallized from ethanol to give **5** (0.28 g, 75%): mp 140–141 °C; $[\alpha]^{23}D$ −155° (*c* 0.73, $CHCl_3$); MS *m/e* 236 (M^+); IR (KBr) 2970, 2880, 2820, 1590, 1445, 1433, 1403, 1383, 1362, 1086, 980, 950, 932, 899, 870, 708 cm^{-1}; NMR ($CDCl_3$) τ 3.31 (dd, *J* = 8, 2 Hz, 2 H), 3.74 (dd, *J* = 8, 2 Hz, 2 H), 4.11 (s, 2 H), 6.62–7.63 (m, 8 H), 7.96 (s, 6 H); CD (isooctane), $[\theta] \times 10^{-4}$ (nm) 0 (223), +13.4 (230.5), 0 (240), −5.67 (251.5), −6.02 (261), −0.75 (287), 0 (299), +0.64 (313.5), 0 (330).

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found; C, 91.45; H, 8.53.

(±)-4,7-Dimethyl[2.2]paracyclophane (5). A mixture of *p*-methylbenzyltrimethylammonium bromide (**6a,** 4.0 g) and duryltrimethylammonium bromide[2] (**7a,** 4.3 g) was dissolved in water (100 ml) and treated with freshly prepared silver oxide. To the resulting mixture of quaternary bases, **6b** and **7b,** was added toluene (100 ml) containing phenothiazine (30 mg), and the mixture was heated with stirring. After removal of water by azeotropic distillation, the reaction mixture was refluxed for 3 h. The insoluble polymer was removed from the reaction mixture and the filtrate was concentrated under vacuum. The resulting solid was chromatographed on neutral alumina. Elution with hexane gave [2.2]paracyclophane (**9**), 4,7-dimethyl[2.2]paracyclophane (**5**), and 4,7,12,15-tetramethyl[2.2]paracyclophane.[14] The compound **5** was recrystallized from hexane, 0.35 g (8.4%), mp 151–152 °C.

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 7.53. Found: C, 91.48; H, 8.51.

(*R*)-(−)-4-Trimethylammoniomethyl-7-methyl[2.2]paracyclophane Bromide (8a). A solution of **4b** (87 g) in ether (2 l.) was treated with excess anhydrous trimethylamine. The resulting salt was collected by filtration, washed with ether, and dried to afford **8a** (99 g, 95%). An analytical sample was recrystallized from ethanol–benzene, mp 213–215 °C, $[\alpha]^{20}D$ −94° (*c* 0.72, CH_3OH).

Anal. Calcd for $C_{21}H_{28}NBr$: C, 67.37; H, 7.54; N, 3.74; Br, 21.35. Found: C, 67.51; H, 7.62; N, 3.71; Br, 21.46.

(*R*)-(−)-Triple-Layered (10) and (*R,R*)-(−)-Quadruple-Layered [2.2]Paracyclophane (11). A mixture of *p*-methylbenzyltrimethylammonium bromide (**6a,** 2.8 g) and **8a** (4.0 g) was dissolved in water (150 ml) and treated with freshly prepared silver oxide. To the resulting aqueous solution of quaternary bases, **6b** and **8b,** was added toluene (150 ml) containing phenothiazine (50 mg), and the mixture was heated with stirring. After removal of water by azeotropic distillation, the reaction mixture was refluxed for 6 h. The insoluble polymer was removed from the reaction mixture, the resulting filtrate was concentrated to a small volume under vacuum, and the remaining solution was chromatographed on neutral alumina. Elution with hexane–benzene (9:1) gave [2.2]paracyclophane (**9,** 0.11 g, 7%). Further elution with hexane–benzene (5:1) produced (−)-triple-layered [2.2]paracyclophane (**10**) and (−)-quadruple-layered compound (**11**). The compound **10** was recrystallized from hexane: 0.19 g (5%); mp 170–171 °C; $[\alpha]^{28}D$ −256° (*c* 0.67, $CHCl_3$); IR (KBr) 2960, 2880, 2820, 1580, 1491, 1448, 1424, 1183, 925, 901, 862, 707, 678 cm^{-1}; UV (isooctane) λ_{max} 227 sh, 280, 291 sh, 348 nm (log ϵ 4.21, 4.27, 4.22, 2.41); NMR ($CDCl_3$) τ 3.85 (s, 8 H), 4.65 (s, 2 H), 6.8–7.7 (m, 16 H); CD (isooctane) $[\theta] \times 10^{-4}$ (nm) 0 (222.5), −2.77 (226), 0 (230), +9.67 (236), 0 (250), −2.26 (260), −2.59 (272), −5.15 (309), −1.50 (350), 0 (374); MS *m/e* 338 (M^+).

Anal. Calcd for $C_{26}H_{26}$: C, 92.26; H, 7.74. Found: C, 92.28; H, 7.81.

The compound **11** was recrystallized from hexane–benzene: 0.1 g (4%); mp 230–231 °C; $[\alpha]^{21}D$ −285° (*c* 0.39, $CHCl_3$); IR (KBr) 2950, 2880, 2820, 1580, 1492, 1448, 1424, 1184, 924, 880, 866, 788, 707, 685, 668 cm^{-1}; UV (isooctane) λ_{max} 230 sh, 267 sh, 310 nm (log ϵ 4.20, 3.61, 3.27, 2.86); NMR ($CDCl_3$) τ 3.98 (s, 4 H), 4.65 (s, 2 H), 6.8–7.7 (m, 24 H); CD (isooctane) $[\theta] \times 10^{-4}$ (nm) 0 (211), +31.2 (217.5), +26.3 (232.5), 0 (249), −4.59 (260), −6.26 (272), −3.30 (311), −3.97 (339), −2.62 (355), 0 (385); MS *m/e* 468 (M^+).

Anal. Calcd for $C_{36}H_{36}$: C, 92.26; H, 7.74. Found: C, 92.27; H, 7.76.

(±)-Dimethyl Derivative of Triple-Layered [2.2]Paracyclophane (12a). A mixture of quaternary ammonium bromide (**19a**,[12] 50 g), methylbenzyltrimethylammonium bromide (**6a**, 160 g), and water (2 l.) was converted to the hydroxides, **6b** and **19b**, in the usual manner using silver oxide. After removal of the solids, the aqueous solution was evaporated to 500 ml under vacuum. The resulting solution was mixed with toluene (1.3 l.) containing phenothiazine (2 g), and heated to reflux. Water was removed by azeotropic distillation, and the reaction mixture was refluxed for 3 h. After the insoluble polymer was removed from the reaction mixture, the filtrate was concentrated to 200 ml under vacuum. Insoluble polymer and [2.2]paracyclophane were filtered off, and the filtrate was concentrated. The concentrate was chromatographed on neutral alumina with hexane. The resulting product was recrystallized from hexane to give (±)-**12a** (14 g, 33%): mp 175–176 °C; IR (KBr) 2950, 2880, 2820, 1584, 1496, 1453, 1432, 944, 906, 877, 801, 730, 721, 703, 682 cm^{-1}; UV (isooctane) λ_{max} 233 sh, 286 sh, 344 nm (log ϵ 4.11, 3.38, 2.08); NMR ($CDCl_3$) τ 3.80 (s, 4 H), 4.33 (s, 2 H), 4.37 (s, 2 H), 6.80–7.91 (m, 16 H), 8.14 (s, 6 H); MS *m/e* 366 (M^+).

Anal. Calcd for $C_{28}H_{30}$: C, 91.75; H, 8.25. Found: C, 91.71; H, 8.26.

(*R*)-(−)-Dimethyl Derivative of Triple-Layered [2.2]Paracyclophane (12a). The preparation of (−)-**12a** was carried out by the same method described for the preparation of (±)-**12a**, utilizing the quaternary ammonium bromides, **8a** (45 g) and **7a** (120 g). (−)-Dimethyl compound **12a** was purified by column chromatography on neutral alumina and recrystallized from hexane, affording 12.2 g (28%), mp 170–171 °C, $[\alpha]^{21}D$ −241° (*c* 0.46 $CHCl_3$).

Anal. Calcd for $C_{28}H_{30}$: C, 91.75; H, 8.25. Found: C, 91.71; H, 8.27.

(±)-Quaternary Ammonium Bromide (13a). A mixture of (±)-**12a** (13.5 g), *N*-bromosuccinimide (3.5 g), benzoyl peroxide (20 mg), and carbon tetrachloride (300 ml) was heated to reflux for 4 h. After removal of succinimide, the filtrate was concentrated under vacuum. The concentrate was taken up in ether and treated with excess anhydrous trimethylamine to give (±)-**13a** (7.5 g, 82% based on *N*-bromosuccinimide). An analytical sample was recrystallized from water to give the monohydrate, mp >300 °C.

Anal. Calcd for $C_{31}H_{38}NBr{\cdot}H_2O$: C, 72.65; H, 5.90; N, 2.73; Br, 15.59. Found: C, 72.86; H, 5.96; N, 2.66; Br, 15.71.

(*R*)-(−)-Quaternary Ammonium Bromide (13a). The optically active ammonium bromide **13a** (6.8 g, 82% based on *N*-bromosuccinimide) was prepared from (−)-**12a** (12 g) following the method described for the preparation of racemic **13a**. An analytical sample was recrystallized from water to give the monohydrate, mp >300 °C, $[\alpha]^{21}D$ −148° (*c* 0.63, $CHCl_3$).

Anal. Calcd for $C_{31}H_{38}NBr{\cdot}H_2O$: C, 72.65; H, 5.90; N, 2.73; Br, 15.59. Found: C, 72.78; H, 5.93; N, 2.79; Br, 15.69.

(*R,R,R*)-(−)-Quintuple-Layered [2.2]Paracyclophane (14) and (*R,R,R,R*)-(−)-Sextuple-Layered [2.2]Paracyclophane (15). The aqueous hydroxide solution, derived from a mixture of (−)-**13a** (6 g) and (−)-**8a** (4 g), was mixed with toluene (200 ml) and phenothiazine (0.2 g), and then pyrolyzed as described for the preparation of (−)-**10** and (−)-**11**. Insoluble polymers were removed from the mixture and the filtrate was concentrated under vacuum. The resulting solid was chromatographed on neutral alumina. Elution of the column with hexane–benzene (9:1) provided (−)-**11** (0.5 g, 6%). Further elution with hexane–benzene (5:1) produced (−)-**14** (0.13 g, 3%), which when recrystallized from hexane–benzene gave mp >300 °C; $[\alpha]^{22}D$ −362° (*c* 0.22, $CHCl_3$); IR (KBr) 2940, 2890, 2830, 1582, 1497, 1477, 1450, 1425, 1182, 946, 894, 870, 796, 716, 673 cm^{-1}; UV (isooctane) λ_{max} 271 sh, 350 nm (log ϵ 3.90, 2.70); NMR ($CDCl_3$) τ 3.90 (s, 8 H), 4.85 (s, 4 H), 5.00 (s, 2 H), 6.1–8.1 (m, 32 H); CD (isooctane) $[\theta] \times 10^{-4}$ (nm) 0 (211), +42.6 (218), +28.5 (234), 0 (252), −8.11 (271.5), −3.74 (312), −4.47 (343), 0 (390); MS *m/e* 598 (M^+).

Anal. Calcd for $C_{46}H_{46}$: C, 92.26; H, 7.74. Found: C, 92.25; H, 7.76.

Elution with hexane–benzene (1:1) afforded (−)-**15** (0.05 g, 1.4%), which when recrystallized from benzene gave mp >300 °C; $[\alpha]^{16}D$ −420° (*c* 0.24, $CHCl_3$); IR (KBr) 2940, 2890, 2830, 1582, 1495, 1477, 1453, 1425, 1182, 893, 749, 711, 672 cm^{-1}; UV (isooctane) λ_{max} 275 sh, 355 sh nm (log ϵ 3.93, 3.09); NMR ($CDCl_3$) τ 3.94 (s, 8 H), 4.95 (s, 4 H), 5.15 (s, 4 H), 7.0–8.2 (m, 40 H); CD (isooctane) $[\theta] \times 10^{-4}$ (nm) 0 (257), −9.28 (274), −3.97 (310), −5.80 (355), 0 (400); MS *m/e* 728 (M^+).

Anal. Calcd for $C_{56}H_{56}$: C, 92.26; H, 7.74. Found: C, 92.29; H, 7.71.

Preparation of (*R,R,R*)-(−)-[5]Chochin (14) by "Chiral Recognition". The hydroxide solution (100 ml) derived from a mixture of quaternary ammonium bromides, (±)-**13a** (8.8 g) and (−)-**8a** (9.1 g), was pyrolyzed in the usual manner. After removal of the insoluble polymers, the filtrate was concentrated under vacuum and the residual oil was chromatographed on neutral alumina. Elution with hexane–benzene (9:1) gave (−)-**11** (0.4 g, 7%). Further elution with hexane–benzene (5:1) produced (−)-**14** (0.3 g, 3%), mp >300 °C, $[\alpha]^{21}D$ −349° (*c* 0.20, $CHCl_3$). Elution with benzene provided (±)-**15** (30 mg, 0.5%) as sparingly soluble prisms, which when recrystallized from xylene gave mp >300 °C.

Anal. Calcd for $C_{56}H_{56}$: C, 92.26; H, 7.74. Found: C, 92.28; H, 7.73.

Registry No.—**1**, 24351-81-3; **2**, 60582-60-7; **3a**, 32212-95-6; **3b**, 60582-61-8; **4a**, 36325-22-1; **4b**, 36325-23-2; (−)-**5**, 32212-91-2; (±)-**5**, 60582-62-9; **6a**, 16814-21-4; **7a**, 27742-95-6; **8a**, 36659-06-0; **10**, 36757-08-1; **11**, 60619-06-9; (±)-**12a**, 60619-07-0; (−)-**12a**, 60619-08-1; (±)-**13a**, 60619-09-2; (−)-**13a**, 60619-10-5; **14**, 60619-11-6; (−)-**15**, 60619-12-7; (±)-**15**, 60619-13-8; **19a**, 60619-14-9.

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Photolysis and Thermolysis of Some 2-Azido-2′-arylazobiphenyls

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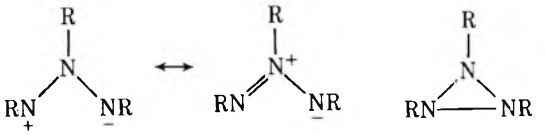
A series of four 2-azido-2′-arylazobiphenyls has been prepared and their photolytic and thermal decomposition investigated in order to throw light on the question whether aryl azides are actually capable of adding to azo compounds by a nonconcerted "nitrene" mechanism and to explore the possible synthetic utility of such additions as a route to benzo[c]cinnoline *N*-arylimides. All four azides exhibit formation of benzo[*c*]cinnoline *N*-arylimides and 4-arylazocarbazoles as major isolable products on photolysis; the same products are apparently formed on thermolysis but removal of the initially formed *N*-arylimides occurs leading to benzo[*c*]cinnoline, thus producing no substantial yields of isolable *N*-arylimides. The reaction products are discussed in terms of a possible nitrene mechanism.

Nitrenes are reactive organic intermediates which can attack multiple bonds and nonbonding electron pairs according to their polar character, giving a great variety of products.[1]

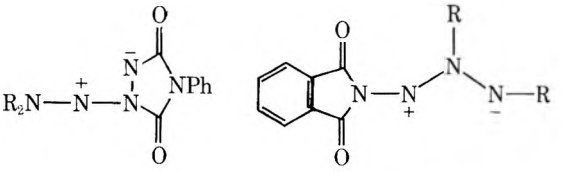
Addition of nitrenes to azo compounds could be in principle the simplest route to azimines (I), the open 1,3-dipolar valence isomers of the unknown triaziridines (II); however, formation



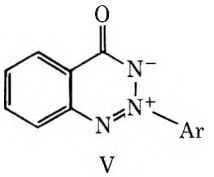
I II

of azimines by reaction of nitrenes (or nitrene precursors) with azo compounds has been positively established only in a few cases.

A number of nucleophilic aminonitrenes have in fact been shown to add smoothly to azoalkanes and azoarenes, giving *N*-aminoazimines (III–IV, R = alkyl or aryl),[2] but photolysis



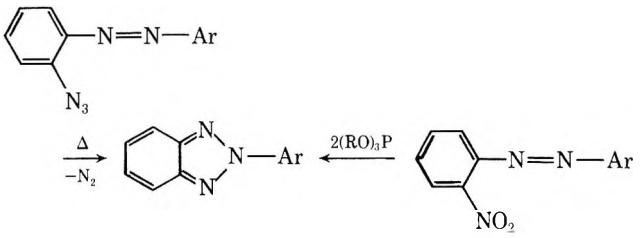
III IV



V

of ethyl azidoformate in the presence of diethyl azodicarboxylate[3] and thermolysis of the same azide in the presence of azobenzene[4] failed to give any isolable azimine, which was postulated as an intermediate to account for the reaction products. Moreover, the cyclic azimine (V, Ar = 4-$NMe_2C_6H_4$) has been reported in very low yield (3%) by reaction of 2-(4′-dimethylaminophenylazo)benzhydrazide with nitrous acid.[4]

So far no clear-cut report on azimine formation by addition of arylnitrenes or their precursors to azo compounds is available in the literature and the question whether arylnitrenes are actually capable of adding to azo compounds is still open. Thermal decomposition of 2-azidoazobenzenes[5] and deoxygenation of 2-nitroazobenzenes by triethyl phosphite[6] are formal intramolecular addition examples of arylnitrenes to azobenzenes.



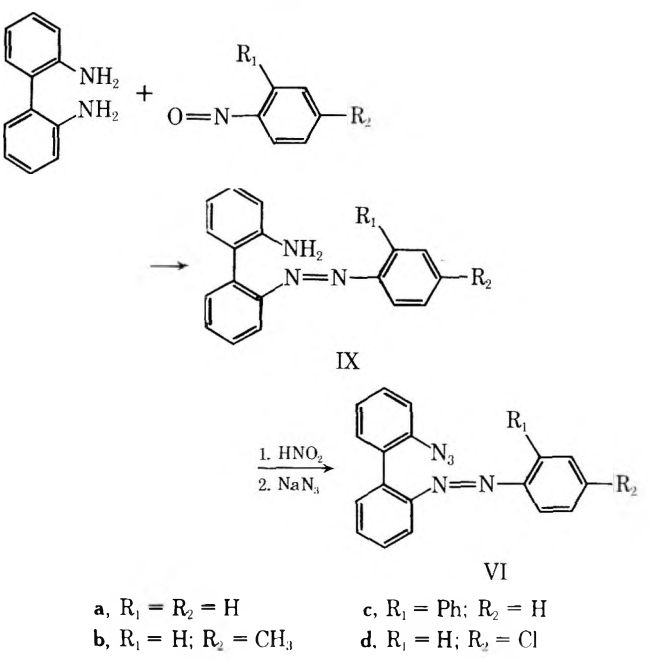
These reactions always result in cyclization to give 2-substituted benzotriazoles, most probably without the actual intermediacy of nitrenes. Cyclization by a concerted process appears in fact much more plausible to account for the low reaction temperatures and the absence of other products expected from nitrene intermediates.[7] On the other hand, isolation of azobenzenes in good yields from reactions producing arylnitrenes would suggest that the reactivity of these nitrenes toward azobenzenes cannot be high.[8] In order to throw light on the reactivity of arylnitrenes (or azides) toward azo compounds and to explore the potential synthetic utility of these reactions as a route to azimines we have investigated the photolytic and thermal decomposition of a number of 2-azido-2′-arylazobiphenyls (VI). In the 2-azido-2′-arylazobiphenyls (VI) the nitrenes that would be derived from the azido group would have the choice of inserting into the C–H bond in the ortho′ position, giving rise to 4-arylazocarbazoles (VII), or adding to the azo group in the other ortho′ position, producing presumably isolable azimines, i.e., benzo[c]cinnoline *N*-arylimides (VIII), a number of which have recently been reported and shown to fairly stable.[9]

Since it is generally accepted that carbazole produced in high yield by either photolysis or thermolysis of 2-azidobiphenyl proceeds from the intermediate 2-nitrenobiphenyl,[10] formation of carbazoles (VII) together with azimines (VIII) (if formed at all) could be construed as diagnostic evidence for the intermediacy of 2-nitreno-2′-arylazobiphenyls (XI) in the decomposition of VI and thus possibly in the formation of *N*-arylimides (VIII).

All starting azides (VI) were most readily prepared from the corresponding amines (IX) by diazotization followed by treatment with sodium azide. Amines (IX) were in turn obtained by condensation of 2,2′-diaminobiphenyl with the appropriate nitrosobenzene derivative. The general procedure is outlined in Scheme I.

Photolysis of azides (VIa–d) with a 100-W high-pressure mercury lamp in benzene solution for ca. 24 h (until TLC showed complete decomposition of starting material) led to the isolation of benzo[c]cinnoline *N*-arylimides (VIIIa–d) (35–40%), 4-arylazocarbazoles (VIIa–d) (10–15%), 2-amino-2′-arylazobiphenyls (IXa–d) (1–2%), and benzo[c]cinnoline (X) (2–4%) as the only identifiable products after column chromatography of the reaction mixtures.

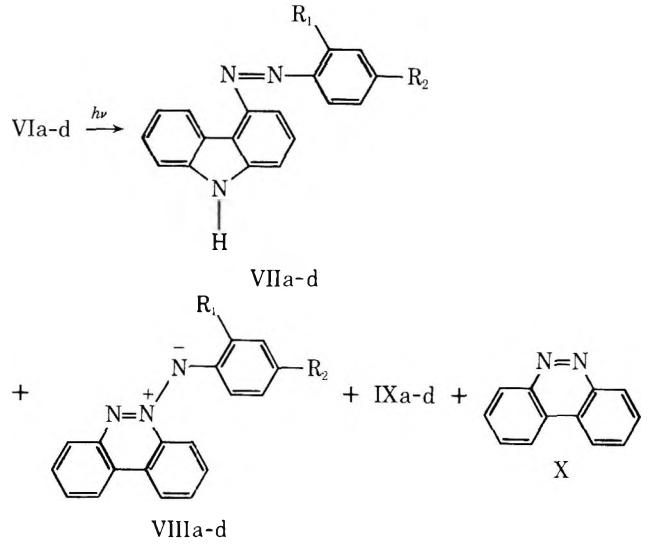
Scheme I



a, $R_1 = R_2 = H$ c, R_1 = Ph; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$ d, $R_1 = H$; R_2 = Cl

Benzo[c]cinnoline *N*-phenylimide (VIIIa) has been previously described.[9] Spectral properties of the new *N*-arylimides (VIIIb–d) were very similar to those of VIIIa. They all show a mass spectral base peak at *m/e* 180 and a low-field one-proton multiplet near δ 8.5–9 in the NMR spectrum, characteristic of the unsubstituted benzo[c]cinnoline *N*-imide[9a] and the isoelectronic benzo[c]cinnoline *N*-oxide.[9a]

Scheme II



The 4-arylazocarbazoles (VIIa–d) were identified on the basis of the elemental analysis and spectroscopic data. In particular they all show the expected sharp N–H stretching absorption at ca. 3460 cm^{-1} in the IR spectrum and a mass spectral base peak at *m/e* 166 corresponding to loss of the arylazo fragment from the parent ion. In the case of VIIc chemical confirmation of the structure was also obtained through hydrogenation of the azo compound to 4-aminocarbazole[11] and 2-aminobiphenyl.

The photolysis products (VII–IX) could be rationalized by postulating the intermediacy of the 2-nitreno-2′-arylazobiphenyls (XI) which undergo intramolecular addition to the azo group to give *N*-arylimides (VIII), intramolecular insertion into the aromatic C–H bond to give carbazoles (VII), and hydrogen abstraction to give amines (IX). Formation of benzo[c]cinnoline (X) can be attributed to photolytic fragmentation of *N*-arylimides (VIII), a general trend encountered with all benzo[c]cinnoline *N*-imides previously reported.[9a] Control experiments showed the *N*-arylmides (VIII) to fragment rather slowly, no more than 10% fragmentation to benzo[c]cinnoline (X) occurring after the same irradiation time employed to bring about complete decomposition of azides (VI). As far as photochemical fragmentation of benzo[c]cinnoline *N*-imides is concerned, a plausible route to benzo[c]cinnoline (X) would be the N–N bond cleavage leading to X and a formal nitrene fragment. Indeed the nitrene fragment has been intercepted in photolysis of the *N*-ethoxycarbonylimide (VIII, $R_1R_2C_6H_3 = CO_2Et$)[9a] but it has never been detected with other *N*-imides examined and in particular no trace of benzofurazan *N*-oxide has been observed in photolysis of the *N*-2,4-dinitrophenylimide (VIII, $R_1 = R_2 = NO_2$).[9a] In our hands the *N*-arylimides (VIIIa–d) proved to fragment to benzo[c]cinnoline and tars, but no evidence of products deriving from nitrene fragments was found. In particular neither carbazole nor azo-2-biphenyl was observed in the photolysis of VIIIc and the nature of the nitrene fragment remains uncertain in these cases.

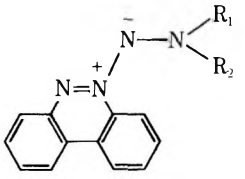
In contrast with photolysis, thermolysis of 2-azido-2′-arylazobiphenyls (VIa–d) in refluxing *o*-dichlorobenzene did not give any isolable benzo[c]cinnoline *N*-arylimides (VIIIa–d). In these cases the major reaction products were benzo[c]cinnoline (X) (34–43%) and 4-arylazocarbazoles (VIIa–d) (8–10%) together with polymeric material. In thermolysis of the azide VIc 2-aminobiphenyl was also isolated in yield comparable to that of X. The formation of benzo[c]cinnoline (X) and the absence of the *N*-arylimides (VIII) could be at first sight most easily explained by thermal fragmentation of the initially formed *N*-arylimides (VIII) incapable of surviving the high-temperature conditions. This "obvious" route to benzo[c]cinnoline (X) was promptly ruled out since *N*-arylimides (VIII) were found to fragment to X very slowly in refluxing *o*-dichlorobenzene, being quantitatively recovered after the same pyrolysis time as employed to effect decomposition of the azides (VI) (ca. 1 h). However, when *N*-arylimides (VIII) were refluxed in *o*-dichlorobenzene in the presence of a slight excess of the corresponding azides VI rapid removal of VIII occurred before decomposition of VI was complete. Moreover, the same results [rapid decomposition to benzo[c]cinnoline (X)] were obtained when the *N*-arylimides VIII were refluxed in the presence of *p*-chlorophenyl azide. In particular with the *N*-imide (VIIIc) 2-aminobiphenyl and benzo[c]cinnoline (X) were obtained in comparable yields. Thus reaction must occur between *N*-arylimides (VIII) and aryl azides (or nitrenes) and this point is under investigation at the present time.

These results would lead to the conclusion that benzo[c]cinnoline (X) isolated in the thermolysis of azides VI derives from reaction of the initially formed *N*-arylimide (VIII) with some reactive species present in the reaction mixture. Complete confirmation of this conclusion was found by carrying out thermolysis of azides VI in refluxing bromobenzene. In this solvent the reaction was rather slow and initial formation of the *N*-arylimides (VIII) could be observed by TLC in each case. In the thermolysis of VIc and VId the corresponding *N*-arylimides VIIIc and VIIId were also isolated by column chromatography after ca. 30% azide decomposition had occurred.

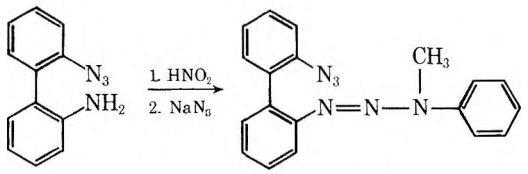
The yields of *N*-arylimides (VIII) were found to decrease rapidly with increasing decomposition of the starting azides (VI). No trace of VIII was left in each case after ca. 50% decomposition of azides VI had occurred.

In order to investigate the possibility of utilizing the intramolecular addition of aryl azides to an azo group as a route to the yet unknown *N*-aminoazimines (XII, R_1 and R_2 = alkyl

or aryl) we prepared the azide XIII. The synthesis of XIII was accomplished by diazotization of the recently reported 2-amino-2′-azidobiphenyl[12] (XIV) and coupling of the diazonium salt with *N*-methylaniline.



XII



XIV XIII

Photolysis of XIII, however, did not furnish any isolable *N*-aminoazimine (XII, $R_1 = CH_3$; $R_2 = Ph$), but carbazole (35%) was obtained together with traces of [c]cinnoline (X), other minor unidentified products, and much polymeric material. The same results were obtained from thermolysis of azide XIII in refluxing chlorobenzene. Formation of carbazole indicates that cleavage of the diazoamino linkage occurs in these reactions. Moreover, the presence of benzo[*c*]cinnoline (X) only in trace amounts and the absence of *N*-aminoazimine (XII, $R_1 = CH_3$; $R_2 = Ph$) would suggest that the cleavage of the diazoamino linkage takes place presumably before decomposition of the azido group.

The results obtained from photolysis and thermolysis of 2-azido-2′-arylazobiphenyls (VI) indicate that, at least in these cases, "azimines" are indeed formed by addition of aryl azides to azo compounds, presumably through the intermediacy of nitrenes, if (a) formation of 4-arylazocarbazoles (VII) [and 2-amino-2′-arylazobiphenyls (IX)], (b) normal decomposition temperatures shown by azides VI (>140 °C), and (c) irreversible formation of *N*-arylimides (VIII) which are not converted thermally or photolytically into VII (and IX) are assumed to provide evidence for the intermediacy of 2-nitreno-2′-arylazobiphenyls (XI) in the decomposition of azides VI and thus in the formation of the *N*-arylimides (VIII). However, the possibility that a nitrene mechanism, leading to VII (and IX), may be in competition with a concerted cyclization mechanism, leading to VIII, in which the azo group provides anchimeric assistance for the elimination of nitrogen, cannot be completely excluded at present and further studies are needed to throw full light on this point as well as on the spin states of nitrenes involved in these cyclizations.

Finally we wish to point out that photolysis of 2-azido-2′-arylazobiphenyls (VIII) appears to provide a general synthetic route to benzo[c]cinnoline *N*-arylimides (VIII) alternative to those previously reported in the literature.[9]

Experimental Section

All melting points are uncorrected. Reaction products such as benzocinnoline and carbazole were always characterized by mixture melting point determination and IR spectral comparison with authentic commercial samples. IR and NMR spectra are for solutions in carbon disulfide unless otherwise stated. Nitrosobenzene and 4-chloronitrosobenzene were commercial products; 2-nitrosobiphenyl[13] and 4-methylnitrosobenzene[14] were prepared as described in the literature.

Preparation of 2-Amino-2′-arylazobiphenyls (IXa–d). The condensation of 2,2′-diaminobiphenyl with nitrosobenzene, 4-methylnitrosobenzene, 2-nitrosobiphenyl, and 4-chloronitrosobenzene was accomplished by means of the following general procedure.

2-Amino-2′-phenylazobiphenyl (IXa). Nitrosobenzene (8.00 g) in dichloromethane (20 ml) was added over 10 min to a solution of 2,2′-diaminobiphenyl (12.20 g) in a 2:1 mixture of acetic acid and dichloromethane (100 ml). The resulting solution was heated on a steam bath for 20 min, then poured into an excess of water and basified with sodium carbonate. Extraction with ether and evaporation of the extracts left an oil residue which was chromatographed on silica gel. Elution with pentane afforded unreacted nitrosobenzene. Elution with 5% ether–pentane afforded the product (IXa) (7.00 g, 40%) as a red, thick oil which after standing for a few days at 0 °C solidified: mp 58–59 °C; IR ν_{max} 3480 and 3400 cm^{-1} (NH_2); mass spectrum *m/e* 273 (M^+), 257, 181, 167.

Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.84; H, 5.65; N, 15.56.

2-Amino-2′-(4-tolylazo)biphenyl (IXb) was obtained in 38% yield: mp 59–61 °C; IR ν_{max} 3470 and 3380 cm^{-1} (NH_2); mass spectrum *m/e* 287 (M^+), 271, 181, 167, 91.

Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.97; N, 14.62. Found: C, 79.00; H, 5.85; N, 14.40.

2-Amino-2′-(2″-biphenylylazo)biphenyl (IXc) was obtained in 35% yield as a red, thick oil which did not solidify: IR ν_{max} 3463 and 3375 cm^{-1} (NH_2); mass spectrum *m/e* 349 (M^+), 333.

Anal. Calcd for $C_{24}H_{19}N_3$: C, 82.49; H, 5.48; N, 12.03. Found: C, 81.75; H, 5.60; H, 11.85.

2-Amino-2′-(4-chlorophenylazo)biphenyl (IXd) was obtained in 45% yield: mp 86–87 °C; IR ν_{max} 3470 and 3380 cm^{-1} (NH_2); mass spectrum *m/e* 307 (M^+), 291, 181, 167.

Anal. Calcd for $C_{18}H_{14}N_3Cl$: C, 70.24; H, 4.59; N, 13.65; Cl, 11.52. Found: C, 71.00; H, 4.49; N, 13.35; Cl, 11.08.

Preparation of 2-Azido-2′-arylazobiphenyls (VIa–d). The following procedure is typical of that used to prepare azides VIa–d.

2-Azido-2′-phenylazobiphenyl (VIa). A suspension of 2-amino-2′-phenylazobiphenyl (IXa, 1.8 g) in 10 ml of concentrated hydrochloric acid and 30 ml of water was cooled to 0 °C and diazotized by the dropwise addition of 0.5 g of sodium nitrite in 10 ml of water. After standing for 15 min, the resulting solution was treated with 0.8 g of sodium azide in water (10 ml), stirred for 1 h at 0–5 °C, and then extracted with ether. The extracts were dried (Na_2SO_4) and evaporated to give an oily residue which was chromatographed on silica gel. Elution with pentane afforded 1.5 g (80%) of 2-azido-2′-phenylazobiphenyl: mp 43–45 °C; IR ($CHCl_3$) 2120 and 2080 cm^{-1} (N_3); mass spectrum *m/e* 299 (M^+), 271, 270, 257, 219, 180, 152.

Anal. Calcd for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 71.55; H, 4.35; N, 23.10.

2-Azido-2′-(4-tolylazo)biphenyl (VIb) was obtained in 70% yield as red needles: mp 50–52 °C; IR ($CHCl_3$) 2119 and 2085 cm^{-1} (N_3); mass spectrum *m/e* 313 (M^+), 285, 284, 271, 270, 180, 152.

Anal. Calcd for $C_{19}H_{15}N_5$: C, 72.82; H, 4.83; N, 22.35. Found: C, 72.60; H, 4.77; N, 22.46.

2-Azido-2′-(2″-biphenylylazo)biphenyl (VIc). This azide was obtained in 80% yield as orange needles: mp 113–115 °C; IR (CCl_4) 2120 and 2085 cm^{-1} (N_3); mass spectrum *m/e* 375 (M^+), 347, 346, 333.

Anal. Calcd for $C_{24}H_{17}N_5$: C, 76.78; H, 4.56; N, 18.66. Found: C, 76.10; H, 4.62; N, 18.35.

2-Azido-2′-(4-chlorophenylazo)biphenyl (VId). This azide was obtained in 77% yield as orange needles: mp 104–105 °C; IR ($CHCl_3$) 2120 and 2080 cm^{-1} (N_3); mass spectrum *m/e* 333 (M^+), 305, 304, 291, 270, 180, 152.

Anal. Calcd for $C_{18}H_{12}N_5Cl$: C, 64.77; H, 3.63; N, 20.98; Cl, 10.62. Found: C, 64.95; H, 3.52; N, 20.72; Cl, 10.75.

Photolysis of 2-Azido-2′-arylazobiphenyls (VIa–d). General Procedure. Stirred solutions of azides VIa–d (1 g) in 400 ml of benzene were purged with purified nitrogen for 0.5 h and then irradiated at room temperature with a 100-W high-pressure mercury lamp. Progress of the reactions was monitored by TLC and irradiation was stopped after TLC showed absence of starting material (24–36 h). The excess benzene was distilled off and the residue was chromatographed on basic alumina.

Elution was as follows: pentane yielded trace amounts of undecomposed azide; 5% ether–pentane eluted benzo[c]cinnoline *N*-arylimides (VIII); 10% ether–pentane eluted 2-amino-2′-arylazobiphenyls (IX); 20% ether–pentane gave 4-arylazocarbazoles (VII); and 40% ether–pentane yielded benzocinnoline. Continued elution with ether or higher polarity solvent mixtures afforded untractable tarry materials.

Photolysis of 2-Azido-2′-phenylazobiphenyl (VIa). Chromatography afforded (1) trace amounts of unreacted azide and (2) benzo[c]cinnoline *N*-phenylimide (VIIIa, 35%): mp 130–132 °C (lit.[9a] 129–131 °C), identical in all respects with a sample prepared by the method reported by Rees and co-workers;[9a] IR ν_{max} 1934, 1330, 1265, 1135, 755, 710 cm^{-1}; NMR δ 6.8–8.3 (12 H, m) and 8.7–8.95 ppm (1

H, m); mass spectrum *m/e* 271 (M^+), 270, 241, 219, 180, 152.

Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.6; H, 4.8; N, 15.6. Found: C, 79.28; H, 4.91; N, 15.64.

(3) 2-Amino-2′-phenylazobiphenyl (IXa, 2%), identical in all respects with an authentic sample. (4) 4-Phenylazocarbazole (VIIa, 13%), as bright orange needles: mp 190–191 °C; IR ν_{max} 3460 cm^{-1}; mass spectrum *m/e* 271 (M^+), 194, 166, 139, 105, 77.

Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.6; H, 4.8; N, 15.6. Found: C, 78.5; H, 4.8; N, 15.63.

(5) Benzocinnoline (3%).

Photolysis of 2-Azido-2′-(4-tolylazo)biphenyl (VIb). Chromatography afforded (1) trace amounts of unreacted azide and (2) benzo[*c*]cinnoline *N*-(4-tolyl)imide (VIIIb, 36%) as bright orange needles: mp 156–158 °C; IR ν_{max} 1395, 1330, 1265, 1135, 815, 755, 710 cm^{-1}; NMR δ 2.37 (3 H, s), 7–8.3 (11 H, m), and 8.7–8.95 ppm (1 H, m); mass spectrum *m/e* 285 (M^+), 184, 270, 233, 181, 180, 152.

Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.72. Found: C, 79.80; H, 5.33; N, 14.74.

(3) 2-Amino-2′-(4-tolylazo)biphenyl (IXb, ca. 1%), IR identical with that of an authentic specimen. (4) 4-(4-Tolylazo)carbazole (VIIb, 14%): orange-red needles, mp 210–212 °C; IR ν_{max} 3460 cm^{-1} (NH); mass spectrum *m/e* 285 (M^+), 194, 166, 139, 119, 91.

Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.72. Found: C, 79.84; H, 5.31; N, 14.69.

(5) Benzocinnoline (4%).

Photolysis of 2-Azido-2′-(2″-biphenylylazo)biphenyl (VIc). Chromatography gave (1) trace amounts of unreacted azide and (2) benzo[*c*]cinnoline *N*-(2-biphenylyl)imide (VIIIc, 38%): red plates, mp 119–121 °C; IR ν_{max} 1390, 1330, 1265, 1135, 755, 695 cm^{-1}; NMR δ 6.8–8 (16 H, m) and 8.2–8.5 ppm (1 H, m); mass spectrum *m/e* 347 (M^+), 346, 219, 181, 180, 167, 166, 152, 140, 139.

Anal. Calcd for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.83; H, 5.04; N, 12.13.

(3) Violet oily product (≤5%) which rapidly decomposed on standing to give more *N*-imide VIIIc. This unidentified product is likely to be an unstable photoisomer of VIIIc since UV irradiation of pure VIIIc leads to partial conversion of VIIIc to the unknown. (4) 2-Amino-2′-(2″-biphenylylazo)biphenyl (<2%), IR identical with that of an authentic specimen. (5) 4-(2-Biphenylylazo)carbazole (VIIc, 11%): red plates, mp 220–222 °C; IR ν_{max} 3460 cm^{-1} (NH); mass spectrum *m/e* 347 (M^+), 346, 181, 166, 153, 152, 139.

Anal. Calcd for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: 82.50; H, 4.90; N, 12.03.

(6) Benzocinnoline (2%).

Photolysis of 2-Azido-2′-(4-chlorophenylazo)biphenyl (VId). Chromatography afforded (1) a trace of unreacted azide and (2) benzo[c]cinnoline *N*-(4-chlorophenyl)imide (VIIId, 40%): bright orange needles, mp 157–159 °C; IR ν_{max} 1390, 1330, 1268, 1140, 1090, 830, 760, 750, 715 cm^{-1}; NMR δ 6.90–8.00 (11 H, m) and 8.45–8.65 ppm (1 H, m); mass spectrum *m/e* 305 (M^+), 304, 270, 180, 152.

Anal. Calcd for $C_{18}H_{12}N_3Cl$: C, 70.71; H, 3.96; Cl, 11.59; N, 13.74. Found: C, 70.35; H, 3.80; Cl, 11.62; N, 13.85.

(3) 2-Amino-2′-(4-chlorophenylazo)biphenyl (IXd, 2%), identical with an authentic sample. (4) 4-(4-Chlorophenylazo)carbazole (VIId, 13%; red needles, mp 232–233 °C; IR ν_{max} 3470 cm^{-1} (NH); mass spectrum *m/e* 305 (M^+), 304, 166, 139, 111.

Anal. Calcd for $C_{18}H_{12}N_3Cl$: C, 70.71; H, 3.96; Cl, 11.59; N, 13.74. Found: C, 70.48; H, 3.92; Cl, 11.45; N, 13.92.

(5) Benzocinnoline (4%).

Hydrogenation of 4-(2-Biphenylylazo)carbazole (VIIc). The azo compound (50 mg) was dissolved in 50 ml of methanol and hydrogenated using 50 mg of platinum oxide as catalyst. After removal of the catalyst and the excess solvent the residue was chromatographed on basic alumina. Elution with 10% benzene–petroleum ether afforded 2-aminobiphenyl (10 mg), identical with authentic commercial material. Elution with 50% benzene–petroleum gave 4-aminocarbazole (15 mg), mp 190–192 °C (lit.[11] 188–192 °C), *m/e* 182 (M^+).

Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.11; H, 5.50; N, 15.39. Found: C, 78.95; H, 5.35; N, 15.20.

Control Experiments to Determine Photosensitivity of Benzo[*c*]cinnoline *N*-arylimides (VIII). Solutions of *N*-imides VIIIa–d in benzene were irradiated for 36 h, after which time chromatography on basic alumina gave back 90–95% starting material together with benzocinnoline (5–10%). No evidence of products deriving of "nitrene" fragments were found. In particular TLC showed no evidence of carbazole, nor of azo-2-biphenyl or 2-aminobiphenyl from photolysis of the benzocinnoline *N*-(2-biphenylyl)imide (VIIIc).

Thermolysis of 2-Azido-2′-arylazobiphenyls (VIa–d) in *o*-Dichlorobenzene. General Procedure. Solutions of azides VIa–d (1 g) in *o*-dichlorobenzene (40 ml) were refluxed for 1 h, after which time TLC showed that no starting material was left. Dichlorobenzene was distilled off under reduced pressure and the residue was chromatographed on silica gel. Elution was effected with mixtures of ether–pentane as described above for the corresponding photolyses. 2-Azido-2′-phenylazobiphenyl (VIa) gave after thermolysis 4-phenylazocarbazole (VIIa) (9%) and benzocinnoline (34%) as the only identifiable products.

Thermolysis of 2-azido-2′-(4-tolylazo)biphenyl (VIb) afforded 4-(4-tolylazo)carbazole (VIIb, 8%) and benzocinnoline (35%).

Thermolysis of 2-azido-2′-(2″-biphenylylazo)biphenyl (VIc) gave 2-aminobiphenyl (44%), 4-(2-biphenylylazo)carbazole (VIIc, 10%), and benzocinnoline (43%).

From thermolysis of 2-azido-2′-(4-chlorophenylazo)biphenyl (VId), 4-(4-chlorophenylazo)carbazole (VIId, 10%) and benzocinnoline (38%) were isolated.

Control Experiments to Determine Thermal Sensitivity of Benzo[*c*]cinnoline *N*-Arylimides (VIII). The *N*-imides VIIIa–d were quantitatively recovered after refluxing in *o*-dichlorobenzene for 1–2 h. When refluxing was continued for 2–4 days, noticeable formation of benzo[*c*]cinnoline was observed. In one experiment, benzo[*c*]cinnoline *N*-(2-biphenylyl)imide (VIIIc, 50 mg) was heated under reflux for 4 days, yielding after chromatography 10 mg of recovered VIIIc, 12 mg of 2-aminobiphenyl, and 17 mg of benzocinnoline.

When *N*-imides VIIIa–d were refluxed in *o*-dichlorobenzene in the presence of an excess of the coresponding 2-azido-2′-arylazobiphenyls VIa–d (1:2–5 molar ratio) rapid decomposition of the *N*-imides occurred, TLC showing that no trace was left after 1 h refluxing.

Refluxing in *o*-dichlorobenzene of *N*-imides VIIIa–d in the presence of a threefold molar excess of *p*-chlorophenyl azide also led to rapid decomposition of VIIIa–d, benzocinnoline being the only recognizable product. (2-Aminobiphenyl was also formed in the case of the *N*-imide VIIIc.)

Thermolysis of 2-Azido-2′-arylazobiphenyls VIa–d in Bromobenzene. Thermal decomposition of azides VIa–d in refluxing bromobenzene was much slower than in *o*-dichlorobenzene. Qualitative experiments showed that the *N*-imides VIIIa–d were formed at the beginning of the reactions and survived for ca. 2 h after which time the starting azides were considerably unchanged whereas only trace amounts of the *N*-imides were left.

From two experiments carried out on a preparative scale (1 g of starting azide) benzo[c]cinnoline *N*-(2-biphenylyl)imide (VIIIc) (15% yield, 30% decomposition of azide VIc) and benzo[*c*]cinnoline *N*-(4-chlorophenyl)imide (VIIId) (13% yield, 25% decomposition of azide VId) were isolated by chromatography.

***N*-Methyl-*N*-(2′-azido-2-biphenylylazo)aniline (XIII).** 2-Amino-2′-azidobiphenyl[12] (1.9 g) was dissolved in 30 ml of water containing 3 ml of concentrated hydrochloric acid. The solution was cooled to 0 °C and diazotized with 0.7 g of sodium nitrite in 10 ml of water. The diazonium salt solution was filtered into an ice-cold solution of *N*-methylaniline (11 g) in 50 ml of water containing 3 ml of concentrated hydrochloric acid. Sodium acetate (5 g) was added to the solution. After 1 h stirring, the reaction mixture was extracted with ether and the extracts were washed with water, then dried (Na_2SO_4) and evaporated. The residue was chromatographed on alumina (pentane as eluent) to afford 2.25 g of XIII as sulfur-colored plates: mp 48–50 °C; IR ν_{max} 2075 cm^{-1} (N_3); mass spectrum *m/e* 328 (M^+), 300, 222, 195, 181, 180, 166, 152, 139, 106, 77.

Anal. Calcd for $C_{19}H_{16}N_6$: C, 69.50; H, 4.91; N, 25.59. Found: C, 69.72; H, 4.85; N, 25.12.

Photolysis of *N*-Methyl-*N*-(2′-azido-2-biphenylylazo)aniline (XIII). A solution of 1 g of azide XIII in 350 ml of N_2-saturated cyclohexane was irradiated for 5 h, after which time TLC showed the starting material to be absent. Solvent was evaporated and the residue chromatographed on silica gel to give carbazole (35%) together with trace amounts of benzocinnoline and other unidentified products accompanied by much polymeric material.

Thermolysis of *N*-Methyl-*N*-(2′-azido-2-biphenylylazo)aniline (XIII). A solution of 0.5 g of XIII in chlorobenzene was heated under reflux for 6 h. Chlorobenzene was distilled off under vacuum and the residue chromatographed to give carbazole (30%) together with traces of benzocinnoline and much polymeric material.

Registry No.—VIa, 60595-17-7; VIb, 60595-18-8; VIc, 60595-19-9; VId, 60595-20-2; VIIa, 60595-21-3; VIIb, 60595-22-4; VIIc, 60595-23-5; VIId, 60595-24-6; VIIIa, 54507-87-8; VIIIb, 60595-25-7; VIIIc, 60595-26-8; VIIId, 60595-27-9; IXa, 60595-28-0; IXb, 60595-29-1; IXc, 60595-30-4; IXd, 60595-31-5; XIII, 60595-32-6; XIV, 54147-64-7; 2,2′-diaminobiphenyl, 1454-80-4; nitrosobenzene, 586-96-9; 4-

methylnitrosobenzene, 623-11-0; 2-nitrosobiphenyl, 21711-71-7; 4-chloronitrosobenzene, 932-98-9; sodium nitrite, 7632-00-0; 4-aminocarbazole, 18992-64-8.

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Synthesis of 1-α-Cumyl-1,2,3,6-tetrahydropyridazine-3,6-dione

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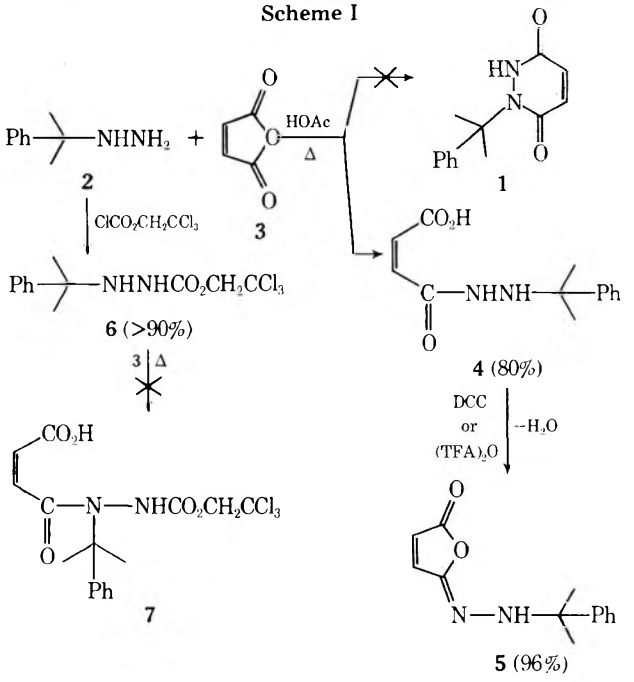
The title compound **1** cannot be prepared from reaction of α-cumylhydrazine (**2**) and maleic anhydride (**3**) in a manner analogous to the preparation of the 1-phenyl analogue. Instead, this reaction affords maleamic acid **4** and, after dehydration, isomaleimide **5**. When the unsubstituted nitrogen of **2** is protected by conversion to the trichloroethyl carbazate **6**, the substituted nitrogen is inert toward maleic anhydride, but not toward the more reactive maleoyl chloride **10**. The latter can be prepared by the reaction of lithium trichloroethoxide with excess maleic anhydride, followed by treatment with phosphorus trichloride. Maleic anhydride, which is unreactive toward 2,2,2-trichloroethanol, affords the isomeric fumarate **9** when treated with excess alkoxide ion. Treatment of carbazate **6** with maleoyl chloride **10** affords maleamate **11**. The latter diectly affords the desired tetrahydropyridazinedione **1** upon treatment with zinc in acetic acid.

1-α-Cumyl-1,2,3,6-tetrahydropyridazine-3,6-dione[1-4] (**1**), a precursor of a cyclic diacylhydrazyl radical which we desired, could not be prepared from α-cumylhydrazine[5] (**2**) and maleic anhydride (**3**). This unsuccessful approach is similar to that used to prepare the analogous 1-phenyltetrahydropyridazinedione[6] from phenylhydrazine. However, in the present case, α-cumylaminomaleamic acid (**4**) is obtained as the only product (Scheme I). Dehydration of **4** with either dicyclohexylcarbodiimide or trifluoroacetic anhydride affords the yellow isomaleimide **5** rather than the desired tetrahydropyridazinedione **1**. NMR chemical shifts (δ 6.13 and 7.20 ppm), vinyl coupling constant (J = 5.5 Hz), and ir carbonyl (1784 and 1757 cm^{-1}) and imine (1618 cm^{-1}) absorption peaks are in agreement with those observed for other isomaleimides.[7]

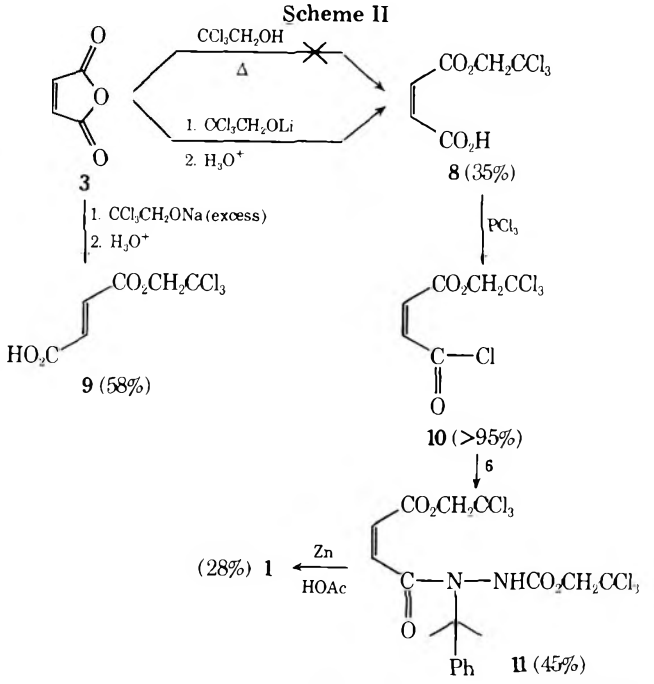
Scheme I



At this point, we felt that if the unsubstituted nitrogen of the hydrazine were protected, the maleic anhydride would be forced to react at the less reactive substituted nitrogen. Trichloroethoxycarbonyl[8] was chosen for this role since it could be removed under mild conditions that would not affect any of the other functionality present. To this end, α-cumylhydrazine was treated with 2,2,2-trichloroethyl chloroformate affording trichloroethyl carbazate **6** as a light, brown oil that could not be crystallized or distilled. The NMR spectrum of the oil is consistent with the assigned structure and showed it to be relatively pure. Reaction of carbazate **6** with maleic anhydride in refluxing toluene for 3 days failed to produce any detectable (NMR) quantity of the desired product **7**; extensive decomposition of the carbazate, however, was indicated.

We thought that a more reactive form of maleic acid could be obtained by protecting one carboxyl group and converting the other to the acid chloride. The trichloroethyl ester was chosen as the protecting group since this would allow removal of both protecting groups in one step. Heating maleic anhydride with trichloroethanol at 100 °C for 1 h (Scheme II) failed to produce any reaction (as judged by NMR), although methanol or ethanol react under these conditions.[9] Continued heating at 150 °C for 5 h afforded a colorless solid having an NMR spectrum inconsistent with that expected of the desired maleate **8**. Treatment of the anhydride with excess sodium trichloroethoxide affords the isomeric trichloroethyl hydrogen fumarate **9** [NMR, J_{vinyl} = 16.1 Hz (trans HC=CH);[10] ir 982 cm^{-1} (trans C=C)[11]]. Presumably, excess alkoxide ion allows the maleate isomerize to the sterically less congested fumarate

Scheme II



through reversible Michael addition to the double bond. When the reaction was carried out using the lithium alkoxide and excess maleic anhydride, the desired trichloroethyl hydrogen maleate **8** [NMR, J_{vinyl} = 12.4 Hz (cis **HC=H**);[10] ir 722 cm^{-1} (cis C=C)[11]] was obtained. Treatment of maleate **8** with phosphorus trichloride[12] affords maleoyl chloride **10** [NMR, J_{vinyl} = 12.0 Hz (cis **HC=CH**[10]] as a colorless, fuming liquid.

Treatment of trichloroethyl carbazate **6** with maleoyl chloride **10** affords maleamate **11** [NMR, J_{vinyl} = 12.0 Hz (cis **HC=CH**)[10]]. Finally, removal of the two protecting groups with zinc in acetic acid provides the desired α-cumyltetrahydropyridazinedione **1** as a colorless solid. NMR (δ 6.72 and 7.07 ppm, J_{vinyl} = 9.8 Hz) and ir (1665 and 1585 cm^{-1}) spectral data are in accord with that reported for other tetrahydropyridazinediones.[7] When heated in a capillary tube immersed in an oil bath, the amorphous solid changes without melting at ca. 220–230 °C into needles which then melt at 315–316 °C dec. When immersed into hot (250 °C) oil, **1** melts, bubbles, solidifies and does not melt again below 300 °C. Presumably, pyridazinedione **1** loses α-methylstyrene to afford 1,2,3,6-tetrahydropyridazine-3,6-dione (lit. mp >300[13a] and 300–310 °C dec[13b]).

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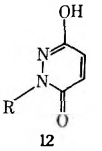
Registry No.—**2**, 3178-39-0; **3**, 108-31-6; **4**, 60498-79-5; **5**, 60498-80-8; **6**, 60498-81-9; **8**, 60498-82-0; **9**, 60498-83-1; **10**, 60498-84-2; **11**, 60498-85-3; **12** (R = α-cumyl), 60498-86-4; 2,2,2-trichloroethyl chloroformate, 17341-93-4; sodium trichloroethoxide, 60498-87-5; lithium trichloroethoxide, 60498-88-6.

Supplementary Material Available. Spectral data (NMR, ir, and mass spectra), elemental analyses, and procedures for the preparation of compounds **1**, **4–6**, and **8–11** (8 pages). Ordering information is given on any current masthead page.

References and Notes

(1) This name and the associated structural formula are used in view of the relationship of **1** to other diacylhydrazines. Numerous studies[2-4] suggest that the structure of **1** would doubtlessly be more accurately portrayed as **12**.



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Synthesis of ω-Methoxy-1,2-dihydronaphthalenes. Gas Phase Pyrolysis of 1-(2′-, 3′-, and 4′-Methoxyphenyl)-1,3-butadienes

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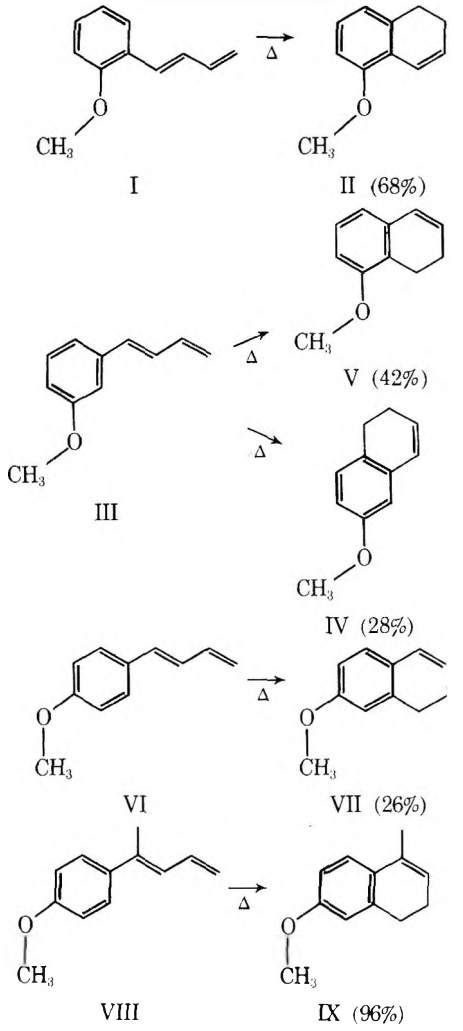
Gas-phase pyrolysis of 1-(2′-methoxyphenyl)-1,3-butadiene yields 5-methoxy-1,2-dihydronaphthalene. Likewise, pyrolysis of 1-(3′-methoxyphenyl)-1,3-butadiene yields a mixture of 6-methoxy- and 8-methoxy-1,2-dihydronaphthalene. Pyrolysis of 1-(4′-methoxyphenyl)-1,3-butadiene yields 7-methoxy-1,2-dihydronaphthalene. Finally, pyrolysis of 2-(4′-methoxyphenyl)-2,4-pentadiene yields 7-methoxy-4-methyl-1,2-dihydronaphthalene. A mechanism for these pyrolysis reactions is discussed.

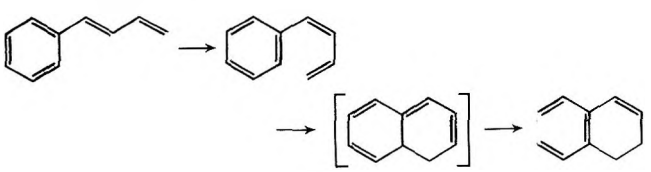
We should like to report the results of the following gas-phase pyrolysis reactions: 1-(2′-methoxyphenyl)-1,3-butadiene (I)[1] yields 5-methoxy-1,2-dihydronaphthalene (II, 68%);[2] 1-(3′-methoxyphenyl)-1,3-butadiene (III)[3] yields a mixture of 6-methoxy-1,2-dihydronaphthalene (IV, 28%)[4] and 8-methoxy-1,2-dihydronaphthalene (V, 42%);[2] 1-(4′-methoxyphenyl)-1,3-butadiene (VI)[1,5] yields 7-methoxy-1,2-dihydronaphthalene (VII, 62%);[6-8] and finally 2-(4′-methoxyphenyl)-2,4-pentadiene (VIII) yields 7-methoxy-4-methyl-1,2-dihydronaphthalene (IX, 96%)[9-13] (Scheme I).

These results are consistent with the three-step mechanism

Scheme I. Thermal Electrocyclic Reactions of 1-(2′-, 3′-, and 4′-Methoxyphenyl)-1,3-butadienes

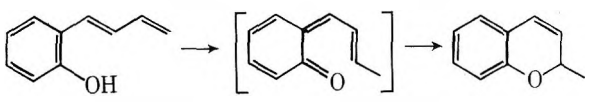


previously proposed to account for the formation of 1,2-dihydronaphthalene on pyrolysis of 1-phenyl-1,3-butadiene in the gas phase.[14] The first step is an isomerization of *trans*-1-phenyl-1,3-butadiene[15] to *cis*-1-phenyl-1,3-butadiene.[16,17] This step is essential since only the cis isomer has the proper geometry to undergo the second step, a thermally allowed disrotatory electrocyclic reaction converting a conjugated triene composed of the two double bonds of the 1,3-butadiene and 2-π electrons from the benzene ring into a 1,3-cyclohexadiene.[18-21] Other examples of participation of 2-π electrons from a benzene ring in thermal electrocyclic reactions have been reported.[22,23] The final step is a 1,5-sigmatropic suprafacial hydrogen migration leading to restoration of the aromatic nucleus.[24]



Previous syntheses of these ω-methoxy-1,2-dihydronaphthalene (ω = 5, 6, 7, or 8) isomers have utilized a variety of reactions since no one reaction was generally applicable.[2,4,8,13,25]

Our interest in the pyrolysis of these 1-(2′-, 3′-, and 4′-methoxyphenyl)-1,3-butadienes came from several sources. We wanted to define the scope and generality of the electrocyclic pyrolysis reaction. The question of whether a methoxy substituent could be tolerated in the phenyl ring did not appear trivial. Thus, previous work had shown that the product of pyrolysis of 1-(o-hydroxyphenyl)-1,3-butadiene was not 1,2-dihydro-5-naphthol but rather 2-methylchromene.[26,27] This result was explained by an initial 1,7-sigmatropic hydrogen shift to yield an ω-vinyl-*o*-quinomethide intermediate which undergoes electrocyclic ring closure to yield 2-methylchromene.[27] Thus, the ability of the reaction to tolerate a methoxy substituent, at least in the ortho position, was not clear. In addition, the ω-methoxy-1,2-dihydronaphthalenes are of interest from a synthetic point of view.[6-8,13]



The starting materials for these electrocyclic pyrolysis reactions were readily prepared. Addition of allylidenetriphenylphosphorane to the 2-, 3-, or 4-anisaldehydes in a Wittig reaction[28] yields the corresponding 1-(2′-, 3′-, or 4′-methoxyphenyl)-1,3-butadienes in a single step, albeit in low yield ($\simeq$30%). Large-scale preparation of 1-(2′-, 3′-, or 4′-methoxyphenyl)-1,3-butadienes were carried out by addition of allyl Grignard reagent to the corresponding 2-, 3-, or 4-anisaldehyde.[29] The product alcohol was dehydrated by distillation from freshly fused $KHSO_4$ in $\simeq$50% overall yield.[5] 2-(4′-Methoxyphenyl)-2,4-pentadiene was prepared starting from 4-methoxyacetophenone. Addition of allyl Grignard reagent gave 2-(4′-methoxyphenyl)-4-penten-2-ol, which was dehydrated by distillation from tosyl chloride in pyridine to yield a 2:1 mixture of VIII and 2-(4′-methoxyphenyl)-1,4-pentadiene.[30] Control experiments showed that 2-(4′-methoxyphenyl)-1,4-pentadiene was unreactive on pyrolysis. Pyrolysis was performed on mixtures of these dienes.

Demethylation of 5-methoxy-1,2-dihydronaphthalene[30] using sodium ethyl mercaptide in dimethylformamide yields 1,2-dihydro-5-naphthol ($\simeq$35%).[2,26,27]

The structures of IV and V obtained from the pyrolysis of III were confirmed by use of $Eu(fod)_3$ NMR shift reagent. $Eu(fod)_3$ behaves as a Lewis acid and thus coordinates to the basic oxygen of these aromatic methyl ethers.[31,32] The effect of $Eu(fod)_3$ on the chemical shift of a particular proton in the substrate is related to the distance and geometry of the proton from the Eu^{3+} ion.[32] Those protons which are closest to the Eu^{3+} ion shift the most.[32] On this basis, we expect downfield shifts for the aromatic protons at C-5 and C-7 in IV. On the other hand, we expect downfield shifts of the aromatic proton at C-7 and the benzylic protons at C-1 in V. Results consistent with these expectations were obtained. For supporting data, plots of the chemical shift of each proton vs. the sum of all the chemical shifts of these protons observed,[33] see supplementary material microfilm edition.

Experimental Section

All reactions were performed under an atmosphere of prepurified nitrogen. Apparatus was flamed dry prior to use. Many of the compounds reported are known; however, spectral properties even of those that are known are meager. For this reason, IR and NMR of all compounds are reported here. IR spectra were recorded on a Perkin-Elmer 337 spectrometer and were calibrated against known peaks in a polystyrene film. NMR spectra were taken in $CDCl_3$ solution on a Varian XL-100 or in CCl_4 solution on a Varian T-60 using Me_4Si as an internal standard. Ultraviolet spectra were taken in spectroquality cyclohexane on a Beckman Acta M spectrometer. GLC was carried out on a Hewlett-Packard F & M 700, using either an 8.5 ft × 0.25 in. 20% polyphenyl ether 6 ring, on Chromosorb P at 190–200 °C (A) or 1.5 ft × 0.25 in. 20% Carbowax on Chromosorb P column at 165 °C (B). Melting points were taken on a Thomas-Hoover instrument and are uncorrected. Microanalyses were performed by Cal. Tech. Analytical Services, Pasadena, Calif.

2-(4′-Methoxyphenyl)-4-penten-2-ol. To a 250-ml three-neck round-bottom flask, equipped with a reflux condenser, pressure-equalizing addition funnel, and overhead stirrer, was added allylmagnesium chloride (Alfa), 1.9 M, in THF, 60 ml (0.13 mol). *p*-

Methoxyacetophenone (MCB), 15.0 g (0.1 mol), dissolved in 50 ml of ether was added dropwise. The mixture was stirred overnight, then hydrolyzed by addition of 100 ml of cold saturated aqueous NH_4Cl. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, and filtered, and the volatile solvent removed by evaporation under reduced pressure. The crude alcohol was distilled from K_2CO_3 through a 9-cm distillation head to yield 15.8 g (82 mmol), 83%, of 2-(4′-methoxyphenyl)-4-penten-2-ol: bp 118 °C (0.02 mm). IR (neat) -OH, 3630–3300; C=C, 1620 cm^{-1}. NMR δ 7.35 (d, 2 H), J = 9 Hz; 6.85 (d, 2 H), J = 9 Hz; 5.64 (dt, 1 H), J = 14, 8 Hz; 5.16 (m, 2 H); 3.79 (s, 3 H); 2.65 (dd, 1 H), J = 13, 7 Hz; 2.44 (dd, 1 H), J = 14, 8 Hz; 2.22 (s, 1H); addition of D_2O caused the signal at δ 2.22 to disappear; 1.52 (s, 3 H).

1-(2′-Methoxyphenyl)-3-buten-1-ol. As above, 2-anisaldehyde (MCB) was converted to 1-(2′-methoxyphenyl)-3-buten-1-ol in 86% yield: bp 82 °C (0.1 mm) [lit. 96 °C (0.32 mm)].[37] IR (neat) -OH, br, 3750–3250; -OCH_3, 2850; C=C, 1600 cm^{-1}. NMR δ 7.07 (m, 4 H); 5.75 (ddt, 1 H), J = 14, 6, 3 Hz; 4.95 (m, 3 H); 3.80 (s, 3 H); 2.45 (m, 3 H). UV λ 2210 Å, ε 3639; λ 2720 Å, ε 2523; λ 2769 Å, ε 2365.

1-(3′-Methoxyphenyl)-3-buten-1-ol. Similarly, 3-anisaldehyde (Aldrich) gave 1-(3′-methoxyphenyl)-3-buten-1-ol in 75% yield: bp 102 °C (0.1 mm) [lit. 96–97 °C (0.30 mm)].[37] IR (neat) -OH, br, 3800–3200; C=C, 1605 cm^{-1}. NMR δ 7.12 (t, 1 H), J = 8 Hz; 6.90–6.70 (br m, 3 H); 5.91–5.37 (br m, 1 H); 5.10 (d, 1 H), J = 18 Hz; 5.7 (d, 1 H), J = 10 Hz; 4.57 (m, 1 H); 3.75 (s, 3 H); 2.71 (br s, 1 H); addition of D_2O caused the signal at δ 2.71 to disappear; 2.44 (t, 2 H), J = 7 Hz.

1-(4′-Methoxyphenyl)-3-buten-1-ol. In the same way, 4-anisaldehyde (Aldrich)led to 1-(4′-methoxyphenyl)-3-buten-1-ol in 76% yield: bp 93–94 °C (0.1 mm) [lit. 102–103 °C (0.35 mm)].[37] IR (neat) -OH, br, 3700–3130; C=C, 1615 cm^{-1}. NMR δ 7.20 (d, 2 H), J = 9 Hz; 6.82 (d, 2 H), J = 9 Hz; 5.93–5.53 (m, 1 H); 5.13 (d, 1 H), J = 12 Hz; 5.08 (d, 1 H), J = 16 Hz; 4.59 (br t, 1 H), J = 6 Hz; 3.74 (s, 3 H); 2.66–2.62 (br s, 1 H); addition of D_2O caused the signal at δ 2.66–2.62 to disappear; 2.44 (t, 2 H), J = 7 Hz.

2-(4′-Methoxyphenyl)-2,4-pentadiene and 2-(4′-Methoxyphenyl)-1,4-pentadiene. Into a 500-ml three-neck round-bottom flask, equipped with reflux condenser and a Teflon-covered magnetic stirring bar, were placed 200 ml of dry pyridine, 10.0 g (52.5 mmol) of p-toluenesulfonyl chloride (Mallinckrodt), and 9.2 g (47.8 mmol) of 2-(4′-methoxyphenyl)-4-penten-2-ol. The mixture was refluxed overnight. Pyridine was removed by evaporation under reduced pressure. The residue was taken up in 250 ml of ether and washed three times with each of the following: 50 ml of 10% H_2SO_4, 50 ml of aqueous K_2CO_3, and 100 ml of H_2O. The organic layer was dried over Na_2SO_4 and filtered, and the volatile solvents removed by evaporation under reduced pressure. The residue was distilled through a 9-cm vacuum-jacketed column to yield a mixture of dienes, 87% yield, bp 77–78 °C (0.05 mm). Analysis by GLC (B) showed the mixture to consist of VIII (65%) and 2-(4′-methoxyphenyl)-1,4-pentadiene (35%).

VIII: IR (neat) C=C, 1665, 1660; CH_3OAr, 1270–1230 cm^{-1}. NMR δ 7.33 (d, 2 H), J = 9 Hz; 6.83 (d, 2 H), J = 9 Hz; 6.8–6.50 (m, 2 H); 5.27 (dd, 1 H), J = 18, 2 Hz; 5.11 (dd, 1 H), J = 10, 2 Hz; 3.79 (d, 3 H), J = 2 Hz; 2.05 (s, 3 H). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.53; H, 8.01.

2-(4′-Methoxyphenyl)-1,4-pentadiene: IR (neat) C=C, 1625; CH_3OAr, 1240 cm^{-1}. NMR δ 7.36 (d, 2 H), J = 9 Hz; 6.84 (d, 2 H), J = 9 Hz; 5.60–5.0 (m, 5 H) 3.80 (s, 3 H); 3.20 (d, 2 H), J = 4 Hz. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.81; H, 7.97.

1-(2′-Methoxyphenyl)-1,3-butadiene (I). Into a 10-ml round-bottom flask equipped with a 9-cm distillation head and a Teflon-covered magnetic stirring bar were placed 4.65 g (26.0 mmol) of 1-(2′-methoxyphenyl)-3-buten-1-ol and 0.7 g (5.26 mmol) of freshly fused $KHSO_4$. The flask was heated under vacuum (0.1 mm). The product was distilled rapidly since polymerization occurs in the flask. I, 2.24 g (14.1 mmol), 54.2%, was obtained: bp 84 °C (0.3 mm) [lit. 140–143 °C (16 mm)].[1] IR (neat) C=C, 1685 cm^{-1}. NMR δ 7.57–6.24 (br m, 7 H), 5.54–5.04 (br m, 2 H), 3.84 (s, 3 H).

1-(3′-Methoxyphenyl)-1,3-butadiene (III). III prepared as above from 1-(3′-methoxyphenyl)-3-buten-1-ol: bp 96 °C (0.4 mm) [lit. 87 °C (2 mm)].[3] IR (neat) C=C, 1601 cm^{-1}. NMR δ 7.26 (s, 1 H); 7.10–6.60 (m, 4 H), 6.43 (d, 1 H), J = 17 Hz; 6.32 (d, 1 H), J = 15 Hz; 5.45 (d, 1 H), J = 15 Hz; 5.28 (d, 1 H), J = 10 Hz; 3.82 (s, 3 H).

1-(4′-Methoxyphenyl)-1,3-butadiene (VI). In the same manner, 1-(4′-methoxyphenyl)-3-buten-1-ol was converted to VI: bp 80 °C (0.2 mm) [lit. 139–140 °C (12 mm)].[1] IR (neat) C=C, 1595 cm^{-1}. NMR δ 7.31 (d, 2 H), J = 9 Hz; 6.83 (d, 2 H), J = 9 Hz; 6.45 (m, 3 H); 5.18 (m, 2 H); 3.79 (s, 3 H).

Wittig Synthesis of 1-(2′-, 3′-, and 4′-Methoxyphenyl)-1,3-butadienes. 1-(2′-, 3′-, and 4′-methoxyphenyl)-1,3-butadienes were synthesized from the corresponding aldehydes via a Wittig reaction. In a 250-ml round-bottom flask, equipped with reflux condenser, pressure-equilizing addition funnel, and a Teflon-covered magnetic stirring bar, were placed 30.0 g (78 mmol) of allyltriphenylphosphonium bromide (Aldrich) and 250 ml of dry ethyl ether. n-Butyllithium in hexane (Alfa), 32 ml, 2.45 M (78.4 mmol), was added dropwise. After 1 h 10.0 g (73.5 mmol) of 3-anisaldehyde (Aldrich) dissolved in 20 ml of ether was added dropwise. The mixture was allowed to stir overnight. The mixture was filtered. The filtrate was dried over anhydrous $MgSO_4$. Solvents were removed by evaporation under reduced pressure. The residue was bulb to bulb distilled at 0.15 mm to yield 3.45 g (21.5 mmol), 29%, of III.

Pyrolysis of the Dienes. Apparatus. A nitrogen inlet was connected to the top of a 10-ml Hershberg constant rate pressure equalizing addition funnel. The bottom of the addition funnel was connected to a 250-cm long (9 mm o.d. by 8 mm i.d.) quartz pyrolysis tube. The pyrolysis tube was wrapped in the form of a 30-turn spiral, 30 cm high. It was heated by a 30 cm long by 2.5 cm diameter tube furnace which had a 10 °C temperature gradient across the oven. The bottom of the pyrolysis column was connected to a 50-ml two-neck pear-shaped flask which was cooled to −78 °C. The second neck was connected to a trap, cooled to −78 °C. N_2 flowed through the system and into a hood. The diene drop rate, 1/10–11 s, N_2 flow rate 1 ml/19 s, and oven temperature were controlled during each pyrolysis. The oven temperature was monitored by a Leeds and Northrup potentiometer using an iron–constantan thermocouple. Upon completion of the pyrolysis, the solvent was distilled from the product mixture through a 13-cm Vigreux column. Yields were calculated based on recovered starting material.

7-Methoxy-4-methyl-1,2-dihydronaphthalene (IX). The diene mixture (1.6 g, 6.6 mmol) from the dehydration of 2-(4′-methoxyphenyl)-4-penten-2-ol dissolved in 9.5 ml of benzene was pyrolyzed at 439 °C. The residue, 1.04 g (6.0 mmol), was shown by GLC (A) to consist of 30% recovered VIII, 7% 2-(4′-methoxyphenyl)-2,4-pentadiene, and 63% IX. IX had the following properties: bp 75 °C (0.1 mm) [lit. 93–94 °C (1 mm)].[13] IR (neat) C=C, 1605; CH_3OAr, 1245 cm^{-1}. NMR δ 7.12 (d, 1 H), J = 9 Hz; 6.69 (m, 2 H); 5.69 (br s, 1 H); 3.79 (s, 3 H); 2.64 (t, 2 H), J = 7 Hz; 2.23 (br m, 2 H); 2.03 (d, 3 H), J = 2 Hz.

5-Methoxy-1,2-dihydronaphthalene (II). I (2.14 g, 13.4 mmol) dissolved in 20 ml of benzene was pyrolyzed at 460–462 °C. The residue was bulb to bulb distilled at 0.08 mm to yield 1.76 g (11.0 mmol). Analysis of GLC (A) showed the product mixture to consist of recovered I (29%), II (62%), and 1-methoxynaphthalene (8%). II had the following properties: bp 66 °C (0.02 mm) [lit. 130–131 °C (0.15 mm)].[3] IR (neat) C=C, 1565; CH_3OAr, 1250 cm^{-1}. NMR δ 7.08 (t, 1 H), J = 8 Hz; 6.72 (m, 3 H); 6.02 (m, 1 H); 3.82 (s, 3 H); 2.76 (t, 2 H), J = 8 Hz; 2.40–2.12 (br m, 2 H).

8-Methoxy-1,2-dihydronaphthalene (V) and 6-Methoxy-1,2-dihydronaphthalene (IV). III (0.86 g, 5.35 mmol) in 9 ml of benzene was pyrolyzed at 469–471 °C. The residue, 0.60 g (3.74 mmol), was separated by preparative GLC (A). V and IV were isolated in a ratio of 1.55:1.

The isomers were distinguished by use of $Eu(fod)_3$ NMR shift reagent. The $Eu(fod)_3$ (Bio-Rad Laboratories) was dried over P_2O_5. A 0.59 M solution of $Eu(fod)_3$ in $CDCl_3$ (10–25 μl) was syringed into a 5-mm NMR tube containing 6.3 mg of V or IV in 0.4 ml of $CDCl_3$/1% Me_4Si. This procedure was continued until 100 μl of shift reagent solution had been added.

V: bp 70 °C (0.04 mm) [lit. 145 °C (23 mm)].[2] IR (CCl_4) C=C, 1570; $ArOCH_3$, 1255 cm^{-1}. NMR δ 7.08 (t, 1 H), J = 7 Hz; 6.75–6.60 (m, 2 H); 6.40 (br d, 1 H), J = 10 Hz; 5.98 (dt, 1 H), J = 10, 4 Hz; 3.82 (s, 3 H); 2.79 (t, 2 H), J = 8 Hz; 2.38–2.12 (m, 2 H).

IV: bp 71 °C (0.1 mm) [lit. 93–95 °C (1 mm)].[4] IR (CCl_4) C=C, 1600; CH_3OAr, 1248 cm^{-1}. NMR δ 7.00 (d, 1 H), J = 7 Hz; 6.64 (m, 2 H); 6.40 (d, 1 H), J = 9 Hz; 6.01 (dt, 1 H), J = 8, 4 Hz; 3.78 (s, 3 H); 2.72 (t, 2 H), J = 8 Hz; 2.39–2.15 (br m, 2 H).

7-Methoxy-1,2-dihydronaphthalene (VII). VI (0.30 g, 1.87 mmol) dissolved in 5 ml of benzene was pyrolyzed at 478–480 °C. The residue was bulb to bulb distilled at 0.05 mm to yield 0.25 g (1.56 mmol) of product mixture. This was shown by GLC (A) to consist of 33% 2-methoxynaphthalene and 67% VII. VII: bp 63 °C (0.1 mm) [lit. 85–95 °C (1 mm)].[6] IR (neat) C=C, 1605; $ArOCH_3$, 1260 cm^{-1}. NMR δ 6.66 (m, 4 H); 5.86 (m, 1 H); 3.73 (s, 3 H); 2.77 (t, 2 H), J = 7 Hz; 2.38–2.03 (br m, 2 H).

1,2-Dihydro-5-naphthol. Dimethylformamide was distilled from BaO and 15 ml was placed into a 50-ml two-neck round-bottom flask equipped with a reflux condenser, septum, and a Teflon-covered magnetic stirring bar. NaH (0.72 g) was added to the flask and the

mixture was allowed to stir for 5 min. Ethanethiol, distilled from CaH_2, was syringed into the cooled (0 °C) reaction mixture. A 1.6:1 mixture of II and I (0.77 g, 3.8 mmol) was syringed into the reaction and heated for 2.5 h at 140–147 °C.

The reaction mixture was cooled, poured into 150 ml of ice water, and extracted with petroleum ether to remove any unreacted II The aqueous layer was acidified with 4 N HCl and extracted with ether (3 × 50 ml). The organic layers were combined, washed with NaCl solution, dried over anhydrous $MgSO_4$, and filtered, and the volatile solvents removed by evaporation under reduced pressure in a hood. Sublimation yielded white needles, mp 69–71 °C (lit. 69.2–70.2 °C).[2] 1,2-Dihydro-5-naphthol: IR (CCl_4) –OH, br, 3600–3400; C=C, 1600 cm^{-1}. NMR δ 7.03–6.55 (br m, 4 H); 6.00 (dt, 1 H), J = 8, 4 Hz; 1.90 (br s, 1 H), 2.75 (t, 2 H), J = 8 Hz; 1.38–1.17 (br m, 2 H).

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Registry No.—I, 60578-56-0; II, 60573-57-1; III, 39677-53-7; IV, 60573-58-2; V, 60573-59-3; VI, 30448-78-3; VII, 52178-91-3; VIII, 60573-60-6; IX, 4242-13-1; *p*-methoxyacetophenone, 100-06-1; 2-(4′-methoxyphenyl)-4-penten-2-ol, 60573-61-7; 2-anisaldehyde, 135-02-4; 1-(2′-methoxyphenyl)-3-buten-1-ol, 24165-67-1; 3-anisaldehyde, 591-31-1; 1-(3′-methoxyphenyl)-3-buten-1-ol, 24165-65-9; 4-anisaldehyde, 123-11-5; 1-(4′-methoxyphenyl)-3-buten-1-ol, 24165-60-4; 2-(4′-methoxyphenyl)-1,4-pentadiene, 60573-62-8; 1,2-dihydro-5-naphthol, 1429-22-7.

Supplementary Material Available. Plots of observed chemical shifts of protons of IV and V (2 pages). Ordering information is given on any current masthead page.

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Preparation and Properties of Small Ring Bis-Annelated Benzenes

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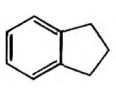
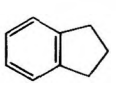
Benzocyclobutene has been prepared by a three-step route involving first the Diels–Alder addition of butadiene to dimethyl cyclobutene-1,2-dicarboxylate. The resulting diester adduct may be hydrolyzed to the corresponding dicarboxylic acid which upon treatment with 2 equiv of lead tetraacetate undergoes bisdecarboxylation and aromatization of the six-membered ring. By substituting different dienes into this scheme, a series of bis-annelated benzene isomers in which the benzene portion was fused to a four- or five-membered ring has been prepared. The ultraviolet and 100-MHz ^1H NMR spectra of these molecules have been reported. In the para-fused series, the chemical shift of the aromatic proton ortho to the fused ring is found to shift upfield with increasing strain. The shift is attributed to a perturbation of the aromatic ring current rather than to inductive effects due to rehybridization at the bridgehead carbon atoms. A shift to longer wavelength absorption in the UV is observed for the para-fused systems as compared to the meta-fused ones. The extinction coefficient is found to increase as the system becomes more symmetrical and more planar.

In 1930 Mills and Nixon proposed that the five-membered ring of indan might sufficiently distort the geometry of the benzene portion of this molecule so that Kekulé resonance form **1a** would be preferred over **1b** and thus partial double



1a

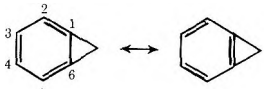


1b

bond fixation might result.[1] Since that time these predictions have been shown to be ambiguous[2] while a theoretical treatment has even been presented which favors structure **1b** over **1a**.[3] Nevertheless, more recent calculations using the CNDO/2 technique[4] as well as an extended Hückel treatment[5] both support a preferred structure in which the bridging bond is lengthened for strained benzocycloalkenes.

There are two fundamental devices whereby one can hope to induce bond localization in an otherwise aromatic molecule: the incorporation of steric strain and the demands of an electronic environment. The latter approach is demonstrated in molecules such as phenanthrene and triphenylene where some bond alteration in the central ring results from the fusion of two or three benzene rings meta to one another. The incorporation of steric strain into an aromatic molecule as a probe of bond localization offers the advantage of not electronically perturbing the cyclic π system. Various structural and spectroscopic studies on the benzocyclopropene[6] and benzocyclobutene system have sought to delineate any bond fixation. X-ray crystallographic data are available for naphthocyclopropene[7] and one derivative of benzocyclopropene.[8] Both studies are inconclusive in that they find the 1,2, the 5,6, and the 1,6 bonds all to be shorter than the C–C bond

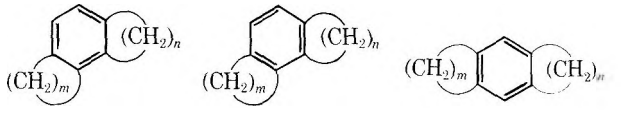
length of benzene (1.39 Å). Thus there appear to be three adjacent short bonds, making it difficult to say anything definite about bond localization in these systems.



2a 2b

Efforts to delineate the effects of fusing a small ring onto the benzene nucleus have led to the presentation of a good deal of chemical, physical, and theoretical data. Vaughn has reported on the behavior of benzocycloalkenes toward electrophilic reagents.[9] Streitweiser points out the increased acidity of benzene protons ortho to a small fused ring.[10] He explains this observation by invoking substantial changes in hybridization at the bridgehead carbons. This viewpoint is corroborated by the earlier metalation studies of Finnegan.[11] Rieke has used the Streitweiser model to explain changes in half-wave reduction potentials[12] and in spin densities[13] of various fused naphthalene systems. Molecular orbital interpretations have provided reasonable correlations with possible hybridization effects.[14,15] Similar theoretical treatments have also been applied to discussions of proton[4,16] and carbon-13[17] NMR data.

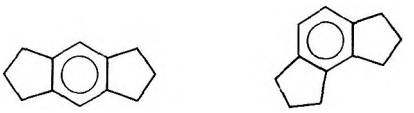
If one assumes that the fusion of a small ring onto the benzene nucleus tends to orient the double bonds such that one of the two Kekulé forms is favored, then it follows that the fusion of two small rings meta to one another would certainly enhance this effect. Thus as the size of the annelated rings is decreased, one resonance form (**3a** or **3b**) should be preferred over the other. When the two small rings are fused para to one another as in **4**, both resonance forms are identical where $m = n$. Any localizing effect of the fused rings must therefore cancel out.



3a 3b 4

The triscycloalkenobenzenes where the fused rings contain from five to eight carbons have been known for some time. A study of their various physical properties has led to the conclusion that when one or more five-membered rings or three six-membered rings are fused to the benzene nucleus, one observes a considerable distortion of the ring current or magnetic anisotropy.[18] A determination of the ionization potentials, UV spectra, and charge-transfer spectra for a series of cycloalkenobenzenes, biscycloalkenobenzenes, and triscycloalkenobenzenes has aided in the investigation of the effect of strain on the π-electron sextet in the ground state as well as higher energy states.[19] In 1960, Cava and co-workers prepared benzo[1,2:4,5]dicyclobutene (**16**)[20] and an x-ray crystal structure of this molecule showed the angles of the benzene ring to be substantially perturbed while the bond lengths of the six-membered ring did not vary significantly.[21] In a preliminary report, we described the preparation of the meta-fused isomer, benzo[1,2:3,4]dicyclobutene (**18**), and pointed out some interesting differences between **16** and **18**.[22] This paper will investigate further the properties of meta and para bis-annelated benzenes.

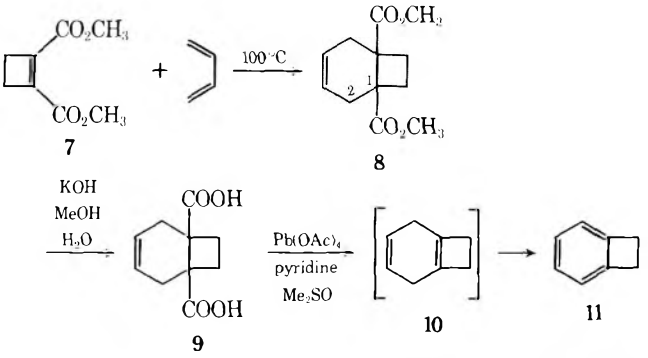
Synthesis of Bis-Annelated Benzenes. Our synthetic objective was to prepare all the bis-annelated benzene isomers in which the benzene portion was fused to a four- or five-membered ring. Of the six possible meta and para isomers, three had been previously reported. Both benzo[1,2:4,5]dicyclopentene[23] (**5**) and benzo[1,2:3,4]dicyclopentene[24] (**6**) have been prepared by cyclizations involving Friedel–Crafts type ring closures. We successfully prepared **5** by the published



5 6

route but had difficulties in the early stages of the syntheses of **6**. It was therefore decided to prepare **6** by an application of our general Diels–Alder approach. Cava and co-workers prepared benzo[1,2:4,5]dicyclobutene (**16**) by the thermal extrusion of two molecules of sulfur dioxide from the corresponding disulfone.[20] Anticipating some possible difficulties with the pyrolysis step, we chose to prepare **16** utilizing our cycloaddition route.

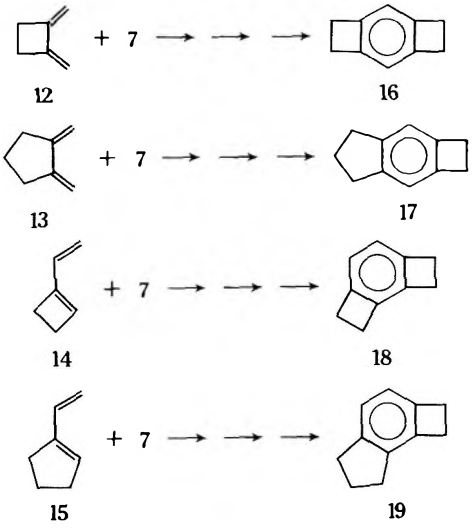
We have recently developed a new approach to the synthesis of benzocyclobutene which is proving most useful in the preparation of annelated derivatives.[25] When butadiene is sealed in a combustion tube with dimethyl cyclobutene-1,2-dicarboxylate for 2 days at 100 °C, the Diel–Alder adduct, **8**, may be obtained in 73% yield.[26] Although both ester functions in **8** are of the neopentyl type, hydrolysis to the corresponding diacid, **9**, may be readily accomplished by refluxing overnight with potassium hydroxide in aqueous methanol. Treatment of **9** with 1 equiv of lead tetraacetate in dimethyl sulfoxide containing 2 equiv of pyridine[27] gives a product which is mainly bicyclo[4.2.0]octa-1(6),3-diene (**10**) contaminated with a small amount of benzocyclobutene (**11**). If the



7 8 9 10 11

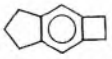
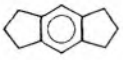
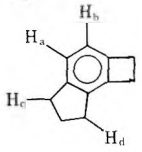
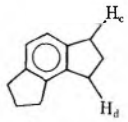
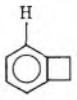
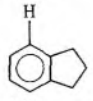
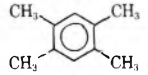
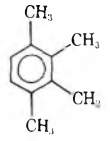
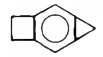
amounts of lead tetraacetate and pyridine are doubled, a 57% yield of **11** may be obtained directly. Under similar oxidizing conditions, 1,4-cyclohexadiene was converted smoothly into benzene.

When dienes **12–15** are substituted for butadiene in the Diels–Alder sequence, the bis-annelated benzenes **16–19** can be obtained. The initial cycloadducts from **14** and **15** show a



12 16
13 17
14 18
15 19

Table I

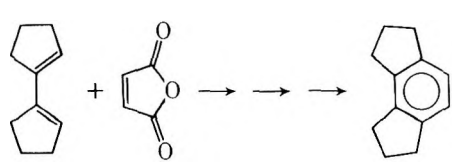
Compd[e]		UV absorption data, nm λ_{max} (95% EtOH) (ϵ)			^{1}H NMR chemical shifts, δ ($CDCl_3$) Ar–H				$J_{C(Ar)-H}$[a]
	16	276 (4570)	280 (5125)	286 (3890)	6.64	2.99			159.9
	17	276 (4070)	280 (4380)	286 (3752)	6.91	3.08	2.86	2.00	158.2
	5	277 (3665)	281 (3785)	287 (3797)	7.08		2.85	2.05	155.4
	18	266 (1360)	269 (1370)	275 (1540)	6.88	3.14			161.0
	19	267 (972)	271 (879)	276 (1037)	H_a 7.07 H_b 6.80	3.12	H_c 2.85 H_d 2.77	2.03	J_{CH_a} = 156.8 J_{CH_b} = 159.4
	6	268 (1008)	272 (870)	277 (1066)	6.95		H_c 2.82 H_d 2.74	1.99	156.9
	11	259 (1380)	265 (2110)	271 (2070)	6.76[b]	3.17			162[c]
	1	259 (889)	266 (1224)	273 (1357)	7.07[b]		2.90	2.04	155.5[c]
	21	268 (712)	273 (654)	278 (727)	6.90		CH_3 2.19		154.0
	22	267 (301)	272 (244)	276 (235)	6.88		1,4-CH_3 2.24 2,3-CH_3 2.17		156.1
	23[d]	284 (1000)	287.5 (1000)	294 (631)	6.85	3.08			

[a] In hertz, experimental error ±1.0 Hz. [b] Reference 17. [c] Reference 34. [d] Reference 31. [e] Registry no. are, respectively, 1610-51-1, 60582-10-7, 495-52-3, 58436-35-4, 50582-11-8, 1076-17-1, 694-87-1, 496-11-7, 95-93-2, 488-23-3, 57867-58-0.

mixture of two products by VPC and NMR. This product mixture could be explained by competing exo and endo modes of Diels–Alder addition which should provide a molecule which is epimeric at the tertiary carbon, C-2. This mixture could be carried through the sequence and had apparently no serious influence on any of the subsequent steps. The hydrocarbon products were readily purified by column chromatography on silica gel by elution with ether–hexane.

Dienes **12** and **13** were prepared by established procedures.[28] We have recently reported the synthesis of 1-vinylcyclobutene (**14**).[22] The addition of vinylmagnesium bromide to cyclobutanone provided 1-vinylcyclobutanol in 66% yield. When this alcohol was heated in the presence of a small amount of iodine crystals, dehydration occurred and 1-vinylcyclobutene was distilled from the mixture in 72% yield. In a similar manner, we have prepared 1-vinylcyclopentene.

Benzo[1,2:3,4]dicyclopentene (**6**) was synthesized by the addition of 1,1′-dicyclopentenyl (**20**) to maleic anhydride,[29]



20 **6**

followed by hydrolysis, decarboxylation, and aromatization under the conditions previously described.

Properties of Bis-Annelated Benzenes. In Table I are compiled some of the spectral properties of the series of bis-annelated benzenes and several related model compounds.

The ^{1}H NMR chemical shifts were assigned without difficulty. For all molecules except **19** the aromatic peak appeared as a singlet. For **19** an AB quartet was observed with J = 7.5 Hz in good agreement with similar ortho couplings.[16] The upfield doublet was assigned to the proton ortho to the four-membered ring based on a recent reassignment of the chemical shifts of benzocyclobutene.[17] The downfield doublet corresponds well with the analogous resonance of indan.

Whether or not the molecule was symmetrical, the cyclobutene ring protons in all cases appeared as a sharp singlet. In the meta-fused cyclopentene systems, however, two overlapping triplets were observed for the benzylic protons in the five-membered ring. The downfield triplet was assigned to the less hindered exterior methylene in accordance with observations made for prehnitene (**22**).[30] In all cases the coupling between cyclopentene methylene protons was 7–7.5 Hz.

A significant trend is evidenced for the aromatic chemical shift of the para-fused series: **16, 17, 5.** With increasing strain the signal moves to higher field, in good accord with assignments for benzocyclobutene and indan. The recently prepared

cyclopropa[4,5]benzocyclobutene (**23**) does not correlate with this trend, exhibiting an aromatic resonance at δ 6.85.[31] In the light of observations by other groups,[16,17] this inconsistency is not unexpected. Consider, for example, the ortho proton of benzocyclopropene which appears at δ 7.15, considerably downfield from what one might expect based only on strain arguments.

It is well known that as the number of alkyl substituents on a benzene ring is increased, the chemical shift of the aromatic protons moves to higher field as a result of shielding due to simple inductive effects.[32] These shifts are also influenced by distortions of the benzene ring geometry caused by steric interactions between the substituent groups. In the series **16, 17, 5,** the inductive effect of the fused rings should remain nearly constant.

A theory has been put forth to explain the enhanced acidity of the aryl positions adjacent to a fused strained ring.[11] It is claimed that for bridgehead carbons "the atomic orbitals used to construct the strained ring have higher p character. Hence, the remaining orbital has higher s character. The ortho-carbon is thus bound to an orbital of higher electronegativity". As the size of the fused ring is decreased the electronegativity of this ortho carbon should increase. The expected effect of this would be to decrease shielding of the attached proton, shifting the resonance to lower field. What is observed for the series **16, 17, 5** as well as for indan and benzocyclobutene is instead a shift to *higher field.*

A sensitive probe of hybridization is the ^{13}C–H coupling constant. Increase in this coupling constant may be taken as an indication of increasing s character of the carbon orbital used in forming the bond.[33] In Table I are recorded the values of $J(^{13}C–H)$ measured by examining the carbon-13 satellites of the aromatic peak in the ^1H NMR spectra. For the series of compounds **16, 17, 5** as well as the series **18, 19, 6** the coupling constant is seen to increase as the size of the fused rings decreases. This observation lends support to the above argument for rehybridization with increasing s character of the ortho C–H bond. There still exists, however, an apparent dichotomy in the correlation between increased shielding at the ortho carbon and increase in $J(^{13}C–H)$. This inconsistency has been pointed out by Günther[34] and more recently by Kitching.[17]

The NMR behavior of strained benzocycloalkenes can be explained by postulating that two electronic effects are operating simultaneously. It has been well documented that there is a localized electronegativity effect which seemingly results from changes in hybridization of the aromatic carbon atoms due to increasing strain.[10-15] The increased shielding of the aromatic protons, however, may be caused by a perturbation of the ring current resulting in a decrease in the diamagnetic anisotropy of the molecule. It is noteworthy that the position of fusion of two small rings to the benzene nucleus is of importance in determining the magnitude of this effect. In the most strained examples of **16** and **18,** the deshielding is more pronounced for the para-fused isomer. In the higher homologues, however, this difference is less well defined and even reversed for **5** and **6.**

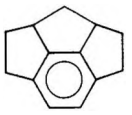
These same two opposing effects are reflected to a lesser degree in the chemical shifts of the benzylic protons. As expected, the cyclobutenyl protons resonate at lower field than the cyclopentenyl ones since they are bonded by orbitals having more s character. Anisotropic deshielding effects are much less strongly felt at benzylic positions owing to the increased distance of the protons from the aromatic ring. Nevertheless the decrease in the cyclobutenyl chemical shift for the series **11, 17, 16** is in line with increased shielding which might result from partial disruption of the aromatic ring current. Once again the meta isomers appear to be less sensitive to this sort of anisotropic perturbation.

For the ethanol solution ultraviolet spectra of the compounds listed in Table I, a broad absorption band may be observed in which at least three vibrational bands can be detected. The λ_{max} and extinction coefficients for these bands have been recorded and two important trends are evidenced.

In considering durene (**21**) and prehnitene (**22**), the λ_{max} are very similar indicating that for unstrained systems the substitution pattern of 1,2,3,4 vs. 1,2,4,5 has little influence on the electronic properties of the molecule. The meta-fused isomers **18, 19,** and **6** all correspond well with the tetramethylbenzenes. For the para-fused isomers, however, a consistent shift of 9–11 nm to longer wavelength is observed. Such shifts previously have been attributed to increased strain. Our data indicate that it is the position at which this strain is introduced into the benzene ring which is critical in perturbing the electronic nature of the molecules. From the longest wavelength 0–0 band, it can be deduced that the energy separation between the ground and first excited state of para-fused benzenes is less (~3.5 kcal/mol) than that for meta-fused benzenes. Such a difference may be due to a less stable ground state or a more stable excited state. Again the data for **23** are out of line with its higher homologues with the shift being in the direction of still longer wavelength.

The extinction coefficients for durene are 2–3 times greater than those for prehnitene. A similar increment is observed when comparing para- to meta-fused bis-annelated benzenes. An increment in extinction coefficient is also observed as the size of the fused rings is decreased. Such changes have often been associated with increased strain.

We have suggested that increased strain in the series **5, 17, 16** may perturb the magnetic anisotropy of the aromatic ring. It is not evident, however, that such strain should directly influence the allowedness of an electronic transition (ϵ). Arnold has put forth an explanation for the higher extinction coefficient of indan over tetralin.[35] He claims that out-of-plane vibrations in the less planar tetralin system provide for poorer overlap between electronic states leading to a less likely transition. Thus the magnitude of the extinction coefficient is more strongly linked to the planarity of the ground state than to the strain inherent in the molecule. The case is well illustrated by comparing **6** (ϵ 1066) with the much more highly strained **24** (ϵ 470).[24,36] The lower extinction coefficient for



24

24 can be explained by the lack of planarity or puckered conformation imposed by the additional fused ring.[37]

Experimental Section

Dimethyl sulfoxide was distilled under vacuum from lithium aluminum hydride. Pyridine was distilled from barium oxide. Just prior to use, lead tetraacetate was recrystallized from acetic acid and dried under vacuum, protected from oxygen and light. Proton magnetic resonance spectra were obtained on a Varian Associates T-60 or XL-100[38] spectrometer and chemical shifts are reported in parts per million downfield from Me_4Si. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Ultraviolet spectra were obtained on a Cary 14 spectrometer. All melting points are uncorrected.

Dimethyl Bicyclo[4.2.0]oct-3-ene-1,6-dicarboxylate (8). In a heavy wall glass tube were placed 3.93 g (0.023 mol) of dimethyl cyclobutene-1,2-dicarboxylate (**7**),[39] 0.04 g of hydroquinone, and 6 ml (excess) of condensed butadiene. The tube was sealed and heated in an oil bath to 100 °C for 48 h. The tube was then cooled and opened and the crude product was flash distilled to provide 3.76 g (73%) of **8,** bp 67–69 °C (0.03 mm): NMR (CCl_4) δ 5.98 (d of d, 2 H, C=CH–), 3.60 (s, 6 H, CO_2CH_3), 2.6–2.1 (m, 6 H), and 1.7 ppm (m, 2 H); IR (thin film) 2930, 1705, 1410, 1130, 1095, 1065 and 985 cm^{-1}.

***Bicyclo[4.2.0]oct-3-ene-1,6-dicarboxylic Acid* (9).** To a solution of 3.66 g (15.9 mmol) of diester **8** in 55 ml of methanol was added a solution of 5.6 g (0.10 mol) of potassium hydroxide in 5 ml of water. The mixture was refluxed overnight, poured into 200 ml of water, and acidified with concentrated hydrochloric acid. The aqueous solution was extracted with ether and the extracts were dried over sodium sulfate. Filtration, removal of solvent, and drying under vacuum provided 2.48 g (80%) of the diacid **9**, mp 149–151 °: NMR (Me_2SO-d_6) δ 11.5 (broad s, 2 H, COOH), 6.0 (m, 2 H, C=CH–), 2.6–2.1 (m, 6 H), and 1.8 ppm (m, 2 H); IR (KBr) 2950, 1708, 1410, 1300, 1254, 1152, and 1095 cm^{-1}.

Bicyclo[4.2.0]-octa-1(6),3-diene (10). To a solution of 0.196 g (1.0 mmol) of **9** and 0.158 g (2.0 mmol) of freshly distilled pyridine in 5 ml of dry Me_2SO under nitrogen was added 0.488 g (1.1 mmol) of lead tetraacetate. An exothermic reaction was observed and the reaction mixture was stirred at room temperature for 3 h. The mixture was then poured into 15 ml of water and extracted five times with ether. The ether solution was dried over potassium carbonate and filtered, and the solvent removed on the rotary evaporator to afford 40.3 mg of crude product. Analysis by VPC (10 ft × 0.25 in 10% Carbowax 6000 on Chromosorb W 60/80 at 113 °C and 30 ml/min) showed **10** at 8.4 min (77%) and benzocyclobutene (**11**) at 12.2 min (23%). The assignments were verified by NMR (CCl_4) δ 7.0 (m, ArH of **11**), 5.65 (s, C=CH of **10**), 3.15 (s, $ArCH_2$ of **11**), and 2.50 ppm, (s, allylic CH_2 of **10** which are coincidently equivalent).

***Benzocyclobutene* (11).** To a solution of 1.96 g (10 mmol) of **10** and 3.16 g (40 mmol) of pyridine in 30 ml of dry Me_2SO under nitrogen was added 9.76 g (22 mmol) of lead tetraacetate. An exothermic reaction was observed with considerable gas evolution. The temperature was maintained at 35 °C with ice bath cooling. After stirring for 3.5 h, the reaction mixture was poured into 120 ml of water and extracted five times with ether. The ether solution was dried over potassium carbonate and filtered, and the solvent removed on the steam bath by distillation through a Vigreux column. Bulb-to-bulb distillation of the residue afforded 0.591 g (57%) of **11** which showed a single major peak by VPC (10 ft × 0.25 in Carbowax 6000 on Chromosorb W 60/80 at 125 °C and 30 ml/min): NMR (CCl_4) δ 6.96 (m, 4 H) and 3.14 ppm (s, 4 H); IR (thin film) 2925, 1745, 1463, 1440, 1117, and 785 cm^{-1}.

1-Vinylcyclobutanol. Vinylmagnesium bromide was generated according to the procedure of Seyferth.[40] A dry, three-neck, 250-ml flask under a nitrogen atmosphere was equipped with a mechanical stirrer, dry ice condenser, and small addition funnel. The apparatus was charged with 7.29 g (0.30 mol) of magnesium metal and 25 ml of dry THF. In the addition funnel was placed a solution of 37.5 g (0.350 mol) of vinyl bromide in 75 ml of dry THF and about 2 ml of this solution was added to the flask with very rapid stirring to initiate the reaction. After initiation, the remaining vinyl bromide was added slowly to maintain a gentle reflux. Once all the magnesium had been consumed, the mixture was cooled to 35 °C and a solution of 14.0 g of cyclobutanone in 30 ml of dry THF was added slowly. The dry ice condenser was replaced by a normal condenser and the solution was refluxed for 90 min. After the flask was cooled to 35 °C, 40 ml of saturated ammonium chloride was added dropwise with additional cooling and vigorous stirring to effect hydrolysis of the magnesium salts. These salts were collected by suction filtration and washed well with anhydrous ether. The combined filtrate was dried over magnesium sulfate and filtered and the solvent removed on the rotary evaporator. Distillation afforded 12.89 g (66%) of 1-vinylcyclobutanol: bp 67–68 °C (45 mm) [lit.[41] bp 49–50 °C (15 mm)]; NMR (CCl_4) δ 6.3–4.9 (ABX pattern, 3 H, CH_2=CH–), 4.0 (broad s, 1 H, OH), and 2.2–1.4 ppm (m, 6 H, $-CH_2-$); IR (thin film) 3360, 2290, 1246, 1150, and 920 cm^{-1}.

1-Vinylcyclobutene (14). In a 15-ml round-bottom flask were placed 6.45 g (0.066 mol) of 1-vinylcyclobutanol and 0.40 g of iodine crystals. The mixture was distilled at atmospheric pressure with magnetic stirring through a Claisen-type distillation head equipped with a 3-in. Vigreux section. After removal of water from the distillate, VPC analysis (Carbowax 20M, 70 °C) showed about 30% unreacted alcohol. This diene–alcohol mixture (4.73 g) was combined with 0.20 g of iodine crystals and redistilled through the same stillhead to afford 3.78 g (72%) of 1-vinylcyclobutene which showed only a single peak by VPC: bp 82 °C (760 mm); NMR (CCl_4) δ 6.5–4.9 (ABX pattern, 3 H, CH_2=CH–), 5.83 (m, 1 H, C=CH), and 2.5 ppm (m, 4 H, $-CH_2-$); IR (thin film) 3045, 2920, 1574, 984, 903, 846, and 767 cm^{-1}.

Bis-annelated benzenes were prepared following the procedures described above for benzocyclobutene. Details concerning amounts of reagents, yields, and physical properties of the intermediates and final products are given below.

Benzo[1,2:4,5]dicyclobutene (16). The reaction of 3.16 g (0.04 mol) of 1,2-dimethylenecyclobutane[28a] with 6.48 g (0.04 mol) of **7** at 80 °C for 20 h gave a product which appeared to contain a good deal of polymer. The ether-soluble portion was chromatographed on 60/200 mesh silica gel eluting with 5:95 ether/petroleum ether to provide 1.58 g (16%) of solid diester adduct, mp 137–142 °C: NMR (CCl_4) δ 3.66 (s, 6 H, CO_2CH_3), 2.6–2.0 (m, 10 H), and 1.7 ppm (m, 2 H); IR (thin film) 2878, 2864, 1742, 1436, 1288, 1125, and 1094 cm^{-1}. Hydrolysis of 1.46 g (5.8 mmol) of the diester with 2.28 g (40 mmol) of KOH in 2 ml of water and 30 ml of methanol provided 1.21 g (93%) of the corresponding dicarboxylic acid,[42] mp 86–89 °C: NMR (Me_2SO-d_6) δ 2.5 (broad s, 4 H, cyclobutenyl H), 2.3 (m, 6 H), and 1.7 ppm (m, 2 H); IR (KBr) 3000, 1710, 1405, 1332, and 1290 cm^{-1}. Treatment of 1.11 g (5.0 mmol) of the dicarboxylic acid with 4.88 g (11 mmol) of lead tetraacetate in 20 ml of dry Me_2SO containing 1.20 g (15 mmol) of pyridine afforded 0.40 g (60%) of crude **16**, mp 90–95 °C. Recrystallization from methanol gave a pure sample of **16**: mp 100–101 °C (lit.[24] mp 101 °C); NMR ($CDCl_3$) δ 6.64 (s, 2 H, ArH) and 2.99 ppm (s, 8 H); IR (KBr) 2930, 1451, 1308, 1215, and 875 cm^{-1}; UV (95% ethanol) 276 nm (ϵ 4570), 280 (5125), and 286 (3890).

4,5-Cyclopentenobenzocyclobutene (17). The reaction of 3.16 g (0.034 mol) of 1,2-dimethylenecyclopentane[28b] with 5.71 g (0.034 mol) of **7** at 80 °C for 20 h gave 3.97 g (45%) of the Diels–Alder adduct after chromatography on 100 g of 60/200 mesh silica gel, eluting with 1:3 ether/hexane: NMR (CCl_4) δ 3.65 (s, 6 H, CO_2CH_3), 2.6–2.1 (m, 14 H), and 1.5 ppm (m, 2 H); IR (thin film) 2855, 1725, 1440, 1325, and 1270 cm^{-1}. Hydrolysis of 3.40 g (12.8 mmol) of the diester with 5.8 g (102 mmol) of KOH in 4 ml of water and 50 ml of methanol provided 2.55 g (85%) of the corresponding dicarboxylic acid,[42] mp 145–150 °C: NMR (Me_2SO-d_6) δ 2.5 (m, 4 H), 1.9 (m, 2 H), and 1.55 ppm (m, 2 H); IR (KBr) 3000, 1730, 1424, 1295, 1177, and 900 cm^{-1}. Treatment of 1.18 g (5 mmol) of the dicarboxylic acid with 4.88 g (11 mmol) of lead tetraacetate in 20 ml of dry Me_2SO containing 1.98 g (25 mmol) of pyridine afforded 0.148 g (20%) of **17** after chromatography on silica gel eluting with hexane, mp 32–33 °C: NMR ($CDCl_3$) δ 6.91 (s, 2 H, ArH), 3.08 (s, 4 H), 2.86 (d of t, 4 H) and 2.00 ppm (quintet, 2 H); IR (thin film) 2960, 2930, 1475, 1331, 1210, and 875 cm^{-1}; UV (95% ethanol) 276 nm (ϵ 4070), 280 (4380), and 286 (3752).

Benzo[1,2:3,4]dicyclobutene (18). The reaction of 2.21 g (27.6 mmol) of 1-vinylcyclobutene with 4.70 g (27.6 mmol) of **7** at 110 °C for 13 h gave a crude product which upon analysis by VPC (5 ft × 0.25 in. 1.5% OV-101 on Chromosorb G 100/120 at 180 °C and 30 ml/min) showed very little starting material and two unresolved peaks at longer retention time. This material was chromatographed on 230 g of 60/200 mesh silica gel, eluting with 1:3 ether/hexane, to provide 4.15 g (60%) of the Diels–Alder adduct: NMR (CCl_4) δ 5.5 (m, 1 H, C=CH), 3.64 (s, 3 H, CO_2CH_3), 3.62 (s, 3 H, CO_2CH_3), and 2.8–1.4 ppm (m, 11 H); at 100 MHz the singlet at 3.62 ppm was resolved into two lines; IR (thin film) 2960, 1745, 1736, 1440, and 1126 cm^{-1}. Hydrolysis of 4.00 g (16 mmol) of the diester with 5.6 g (100 mmol) of KOH in 5 ml of water and 50 ml of methanol provided 3.07 g (86%) of the corresponding dicarboxylic acid:[42] NMR (Me_2SO-d_6) δ 9.77 (broad s, 2 H, COOH), 5.60 (m, 1 H, C=CH), and 3.3–1.5 ppm (m, 11 H); IR (KBr) 3000, 1705, 1412, 900, and 414 cm^{-1}. Treatment of 1.11 g (5 mmol) of the dicarboxylic acid with 4.88 g (11 mmol) of lead tetraacetate in 20 ml of dry Me_2SO containing 1.98 g (25 mmol) of pyridine afforded 70 mg of product after chromatography on 38 g of silica gel eluting with 1:4 ether/hexane. This material was shown to be 50% pure by VPC (10 ft × 0.125 in 10% Carbowax 20M on Chromosorb W 60/80 at 100 °C and 30 ml/min). Pure **18** was isolated by preparative VPC, mp 36–36.5 °C: NMR ($CDCl_3$) δ 6.88 (s, 2 H, ArH) and 3.14 ppm (s, 8 H); IR (thin film) 3030, 2972, 2928, 1447, 1423, 1248, and 823 cm^{-1}; UV (95% ethanol) 266 nm (ϵ 1360), 269 (1370), and 275 (1540); mass spectrum (70 eV) *m/e* (rel intensity) 130 (100), 129 (44), 128 (36), 115 (49), and 51 (17). Anal. Calcd for $C_{10}H_{10}$: *m/e* 130.0783. Found: *m/e* 130.0782.

3,4-Cyclopentenobenzocyclobutene (19). The reaction of 5.5 g (0.058 mol) of 1-vinycyclopentene with 7.14 g (0.042 mol) of **7** at 80 °C for 12 h gave 6.69 g (60%) of the Diels–Alder adduct after chromatography on silica gel, eluting with 1:9 ether/hexane: NMR (CCl_4) δ 5.75 (m, 1 H, C=CH), 3.66 (s, 6 H, CO_2CH_3), and 2.9–1.4 ppm (m, 14 H); IR (thin film) 2880, 2825, 1745, 1440, 1240, and 790 cm^{-1}. Hydrolysis of 6.51 g (0.024 mol) of the diester with 7.5 g (0.134 mol) of KOH in 6 ml of water and 35 ml of methanol provided 5.52 g (97%) of the corresponding dicarboxylic acid:[42] NMR (Me_2SO-d_6) δ 10.0 (broad s, 2 H, COOH), 5.8 (m, 1 H, C=CH), and 2.7–1.1 ppm (m, 14 H); IR (KBr) 2960, 1700, 1440, 1410, and 1300 cm^{-1}. Treatment of 5.2 g (0.022 mol) of the dicarboxylic acid with 19.5 g (0.044 mol) of lead tetraacetate in 75 ml of dry Me_2SO containing 7.66 g (0.097 mol) of pyridine afforded 4.52 g of crude product which was determined to be 8.3% pure by VPC (8 ft × 0.25 in. 10% Carbowax 20M on Chromosorb W60/80 at 135 °C and 30 ml/min) giving an overall yield of

12%. Chromatography on silica gel eluting with hexane provided a pure sample of **19**: NMR ($CDCl_3$) δ 7.07 (d, 1 H, J = 7.5 Hz), 6.80 (d, 1 H, J = 7.5 Hz), 3.12 (s, 4 H), 2.85 (t, 2 H), 2.77 (t, 2 H), and 2.03 ppm (quintet, 2 H); IR (thin film) 2950, 2860, 1465, 1448, 1432, 1312, 1243, 1230, and 813 cm^{-1}; UV (95% ethanol) 267 nm (ϵ 972), 271 (879), and 276 (1037).

Benzo[1,2:3,4]dicyclopentene (6). The reaction of 12.3 g (0.092 mol) of 1,1'-dicyclopentenyl[43] with 9.0 g (0.092 mol) of maleic anhydride at 75 °C for 12 h gave an essentially quantitative yield of the Diels–Alder adduct. A sample recrystallized from hexane gave mp 102–103 °C (lit.[29] mp 102–103 °C). Hydrolysis of the diester with 41.1 g (0.73 mol) of KOH in 75 ml of water and 250 ml of methanol gave 20.89 g (90%) of the corresponding dicarboxylic acid, mp 198–208 °C: NMR (Me_2SO-d_6) δ 12.0 (broad s, 2 H) and 3.2–1.4 ppm (m, 16 H); IR (KBr) 3040, 2960, 1710, 1425, 1245, and 423 cm^{-1}. Treatment of 20.0 g (0.08 mol) of diacid with 78.0 g (0.176 mol) of lead tetraacetate in 200 ml of dry Me_2SO containing 27.8 g (0.352 mol) of pyridine afforded 1.57 g (12%) of **6** after chromatography on silica gel eluting with 3:7 ether/petroleum ether, mp 39–40 °C (lit.[24] mp 40–42 °C: NMR ($CDCl_3$) δ 6.95 (s, 2 H, ArH), 2.82 (t, 4 H), 2.74 (t, 4 H), and 1.99 ppm (quintet, 4 H); IR (thin film) 2960, 2900, 1470, 1315, 1200, and 800 cm^{-1}; UV (95% ethanol) 268 nm (ϵ 1008), 272 (870), and 277 (1066).

Benzo[1,2:4,5]dicyclopentene (5). The procedure of Arnold and co-workers[23] was followed. Starting with 23.6 g (0.2 mol) of indan, 7.05 g (25% overall yield) of **5** was obtained, mp 53–55 °C (lit.[23] mp 52–54 °C): NMR ($CDCl_3$) δ 7.08 (s, 2 H, ArH), 2.85 (t, 8 H), and 2.05 ppm (quintet, 4 H); IR (KBr) 2920, 1485, 1440, 1320, 1210, and 865 cm^{-1}; UV (95% ethanol) 277 nm (ϵ 3665), 281 (3785), and 287 (3797).

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Registry No.—**7**, 1128-10-5; **8**, 37490-84-9; **9**, 60582-12-9; **10**, 38325-66-5; **12**, 14296-80-1; **13**, 20968-70-1; **14**, 58436-36-5; **15**, 28638-58-6; **20**, 934-02-1; butadiene, 106-99-0; vinyl bromide, 593-60-2; cyclobutanone, 1191-95-3; 1-vinylcyclobutanol, 17202-79-8; tricyclo[6.2.0.0^{3,6}]dec-1(8)-ene-3,6-dicarboxylate dimethyl ester, 60582-13-0; tricyclo[6.2.0.0^{3,6}]dec-1(8)-ene-3,6-dicarboxylic acid, 60582-14-1; tricyclo[6.3.0.0^{3,6}]undec-1(8)-ene-3,6-dicarboxylate dimethyl ester, 60582-15-2; tricyclo[6.3.0.0^{3,6}]undec-1(8)-ene-3,6-dicarboxylic acid, 60582-16-3; tricyclo[6.2.0.0^{4,7}]dec-1-ene-4,7-dicarboxylate dimethyl ester, 58436-37-6; tricyclo[6.2.0.0^{4,7}]dec-1-ene-4,7-dicarboxylic acid, 58436-38-7; tricyclo[6.3.0.0^{4,7}]undec-1-ene-4,7-dicarboxylate dimethyl ester, 60582-17-4; tricyclo[6.3.0.0^{4,7}]-undec-1-ene-4,7-dicarboxylic acid, 60582-18-5; maleic anhydride, 108-31-6; tricyclo[7.3.0.0^{4,8}]dodec-8-ene-2,3-dicarboxylate dimethyl ester, 60619-05-8; tricyclo[7.3.0.0^{4,8}]dodec-8-ene-2,3-dicarboxylic acid, 60582-19-6; indan, 496-11-7.

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Catalyses of Polymer Complexes. 4. Polysoap-Catalyzed Decarboxylation of 6-Nitrobenzisoxazole-3-carboxylate Anion. Importance of the Hydrophobic Environment in Activation of the Anion

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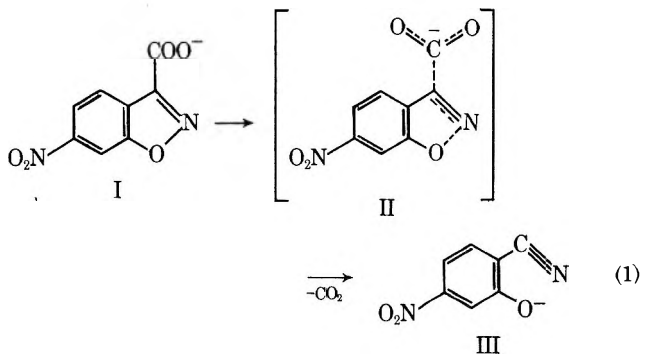
The unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion is markedly catalyzed by cationic polysoaps: partially laurylated poly(4-vinylpyridine) and poly(2-ethyl-1-vinylimidazole). The polymers which acted as efficient catalysts invariably caused the hypsochromic shift of the absorption maximum of methyl orange, and increased dissociation of dichlorophenolindophenol and the fluorescent emission of 1-anilinonaphthalene-8-sulfonate. The linear correlation observed between the logarithm of the rate constant and the wavenumber of the absorption maximum of methyl orange indicates the importance of the hydrophobic environment of polymer micelles in the rate enhancement. The decarboxylation reaction in aprotic solvents, which was performed in connection with the environmental effect of polysoaps, is relatively insusceptible to small amounts of water. The polysoap catalysis can be further enhanced by adding hydrophobic anions and organic solvents (methanol, *tert*-butyl alcohol, acetone). The catalytic efficiency of the polysoap is related to the formation of the hydrophobic domain and the desolvation of the anion is of less importance than in other micelle-catalyzed bimolecular reactions involving oxy anionic nucleophiles.

Electrostatic and hydrophobic interactions are major driving forces for the binding of small molecules to enzymes and cause activation of adsorbed substrates.[1,2] The use of micelles and polyelectrolytes which serve as efficient catalysts for many organic reactions would be among the most expeditious methods to employ these interactions in model enzyme systems.[3,4] Charged polysoaps (polymer micelles) such as poly(vinylpyridines) quaternized by long alkyl chains combine within a molecule structural characteristics of the conventional micelles and polyelectrolytes, and supposedly adopt globular conformations in aqueous media with the hydrophobic region inside and the charged group outside as in some water-soluble proteins.[5,6] The hydrophobicity of polysoap is readily adjustable by changing the content of the long alkyl group. Thus, the charged polysoap would be one of the best model enzyme systems.

The study of the catalytic behavior of polysoaps has been very limited.[7-10] Recently, we found that cationic polysoaps unusually enhanced the nucleophilic reactivity of the bound hydroxamate and thiolate anions toward *p*-nitrophenyl acetate.[10-12] This unusual rate acceleration is largely derived from formation of "*hydrophobic ion pairs*" between anionic nucleophiles and cationic surfactant molecules.[13-15] Unimolecular reactions would be better probes of the environmental effect on the anionic reactivity than bimolecular reactions, since one need not take the proximity term into account. The decarboxylation of carboxylic acids would meet this requirement, since it is unimolecular, almost free from acid and base catalysis, and the rate constants are extremely solvent dependent.[16]

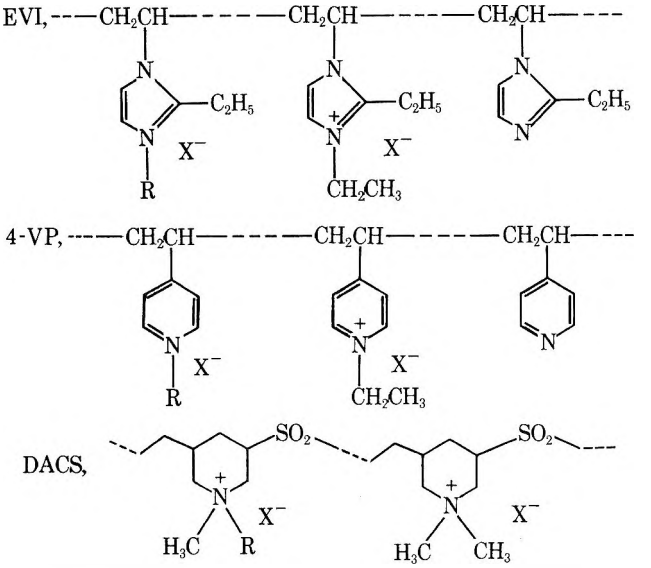
In this paper, we wish to report the polysoap-catalyzed decarboxylation of 6-nitrobenzisoxazole-3-carboxylate anion



(1)

(I) and to discuss the influence of the electrostatic and hydrophobic environments on the reaction rate. The polymers employed are derivatives of poly(2- and 4-vinylpyridines) (2-VP and 4-VP), poly(2-ethyl-1-vinylimidazole) (EVI), and

Polymers:



a copolymer of diallylammonium chloride and SO_2 (DACS). As for example, the polymer abbreviated as EVI-L-9 contains 9 mol % of the lauryl group (for details see Table I).

Experimental Section

Materials. 6-Nitrobenzisoxazole-3-carboxylic acid was prepared according to the method of Borche,[17] and recrystallized from methanol, mp 167–169 °C [lit.[17] 167–169 °C (monohydrate)]. Hexadecyltrimethylammonium bromide (CTAB) and hexadecyltrimethylammonium chloride (CTAC) were purchased from Wako Pure Chemical Industries, and recrystallized from ethanol before use. Proton sponge [1,8-bis(dimethylamino)naphthalene] was the product of Aldrich, and used without further purification.

Preparations of polysoaps from 4-VP, 2-VP, and EVI have been described.[9-11] DACS was kindly supplied by the Nitto-Boseki Co. Research Laboratories for Chemical Fibers.

Purification of Solvents. Acetonitrile and benzonitrile were distilled from phosphorus pentoxide. Benzene was distilled from sodium metal. All the solvents were stored over molecular sieve 5A, and used within 1 week from the day of preparation.

Spectroscopic Measurements. Absorption spectra of methyl orange in the presence of polysoaps were measured on a Hitachi 124

Table I. Composition of Polymers and Several Aqueous Properties

Registry no.	Polymer	Lauryl group content, mol %	Ethyl group content, mol %	$[\eta]$,[a] dl g^{-1}	λ_{max} of methyl orange,[b] nm	K_{DCPI}, M^{-1}
60595-46-2	EVI-L-41	41	49	0.048	433	379
	EVI-L-29	29	67	0.037	417	1207
	EVI-L-9	9	83	0.496	463	~10
59950-02-6	2-VP-L-30	30	~70		427	
59950-03-7	4-VP-L-33	33	48		421	1020
	4-VP-L-22	22	42		440	479
	4-VP-L-12	12	65		449	~30
	4-VP-L-3	3	96		456	
57033-24-6	4-VP-Et-85	0	85		465	
60595-47-3	4-VP-Hx-65	65[c]	0		465	
60595-48-4	4-VP-Bzl-95	95[c]	0		472	
60607-13-8	DACS-LB-22	22[c]	0		437	
	None				465	

[a] 30 °C, μ = 0.02 with KBr; cited from ref 9. [b] 30 °C, pH 9.0, [methyl orange] = 2.50 × 10^{-5} M, [polymer] = (1–3) × 10^{-2} M; partially cited from ref 12. [c] Hx (hexyl group), Bzl (benzyl group), LB (*p*-laurylbenzyl group).

UV–visible spectrophotometer at 30 °C in aqueous solutions adjusted to pH 9.0 with 0.02 M borate buffer. Absorption spectra of dichlorophenolindophenol (DCPI) were obtained at 30 °C in aqueous 0.1 M acetate buffer (pH 3.4). Fluorescence spectra of 1-anilinonaphthalene-8-sulfonate were measured at room temperature by Dr. K. Kano.

Kinetics in Aqueous Systems. The stock solution of I for kinetic measurements in aqueous systems was prepared in ethanol on the day of use. The reaction was initiated by mixing of an aqueous polysoap solution buffered at pH 9.0 with 0.02 M borate with an ethanol solution of I. The progress of the reaction was followed spectrophotometrically at 410 nm (λ_{max} of 2-cyano-5-nitrophenolate, III) using a Hitachi 124 spectrophotometer with a thermostated cell holder. All the kinetic experiments were performed at a calculated ionic strength of 0.01 with KCl unless otherwise stated. The first-order rate constants (k_d) for decarboxylation were determined for up to 4 half-lives (correlation coefficient >0.998).

Kinetics in Organic Solvents. The reaction in organic solvents was initiated by neutralizing the carboxylic function of I by excess proton sponge (ca. three times).

In a rubber-sealed cuvette purged with nitrogen was placed a benzene solution of I and the solution was equilibrated to 30 °C. Then a benzene solution of proton sponge was rapidly added from a syringe, and the reaction was followed spectrophotometrically at 410 nm. The reaction in acetonitrile and benzonitrile was too fast to follow by the conventional spectrophotometer. A stopped-flow apparatus (Union Giken RA-1300), the mixing cell of which is covered with a nitrogen globe, was used for the kinetic measurements. *p*-Toluenesulfonic acid (10 mol % of I) was added to the substrate solution in order to suppress the spontaneous decay of I.

The water content in organic solvents was measured immediately after the reaction with a Hiranuma Aquacounter AQ-1. Several determinations was averaged and the relative error was 5% for benzene and ca. 10% for acetonitrile and benzonitrile.

Surface Tension. Surface tension of aqueous polysoap solutions was measured at room temperature by using a Kyowa Kagaku SR-IV apparatus.

Results

Characterization of Polysoaps. Prior to the kinetic study, several properties of the aqueous polysoap were evaluated. The composition of polysoaps was estimated by both elemental analysis and NMR spectroscopy[9-12] and recorded in Table I. Table I also gives viscosities of the quaternized polymers and absorption spectra of methyl orange measured in the presence of these polymers.

It has been noticed that the intrinsic viscosity of EVI-L-9 is more than ten times larger than those of EVI-L-29 and EVI-L-41.[9] Supposedly, the EVI-L-9 polymer adopts an expanded conformation owing to the electrostatic repulsion like some polyelectrolytes. On the other hand, EVI-L-29 and EVI-L-41 seem to assume compact conformations owing to the hydrophobic aggregation of lauryl groups in spite of the electrostatic repulsion.

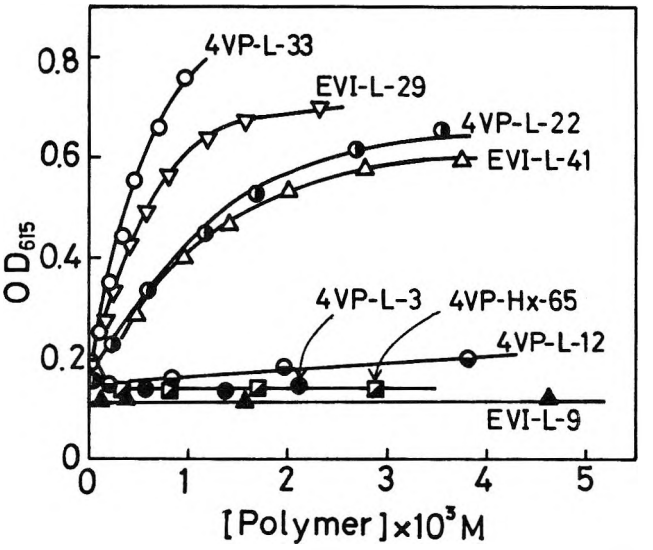


Figure 1. Absorbance of dissociated dichlorophenolindophenol (λ_{max} 615 nm) plotted against the polymer concentration (calculated based on the total concentration of the monomer unit). [DCPI] = (0.96–1.36) × 10^{-4} M, pH 3.4 with 0.1 M acetate.

Visible spectra of methyl orange are frequently employed in order to detect the hydrophobic region present in aqueous media,[18-20] since λ_{max} near 465 nm shifts to shorter wavelengths owing to the hydrophobic environment surrounding the methyl orange molecule. Table I shows that the aqueous solutions of EVI-L-9, 4-VP-L-3, 4-VP-Et-85, 4-VP-Hx-65, and 4-VP-Bzl-95 hardly affected the visible spectra of methyl orange. In contrast, appreciable hypsochromic shifts occurred in the presence of EVI-L-29, EVI-L-41, 2-VP-L-30, 4-VP-L-22, 4-VP-L-33, and DACS-LB-22. The largest hypsochromic shift was observed for EVI-L-29 (417 nm), which is comparable to that in ethanol (418 nm).[21] The polymer which contains more than 10 mol % of the lauryl group appears to form sufficiently hydrophobic domains and causes the spectral shift of adsorbed methyl orange.

2,6-Dichlorophenolindophenol (DCPI) in aqueous acidic solutions is an excellent probe for the micelle formation, the critical micelle concentration (cmc) being detectable based on the color change from light red (undissociated phenol: 517 nm) to blue (phenolate anion: 606 nm).[22] As shown in Figure 1, the polymers with no or small lauryl group contents (less than 12 mol %) little affected the absorption spectrum of DCPI. On the other hand, the absorption band at 615 nm increased with increasing concentrations of EVI-L-41, EVI-

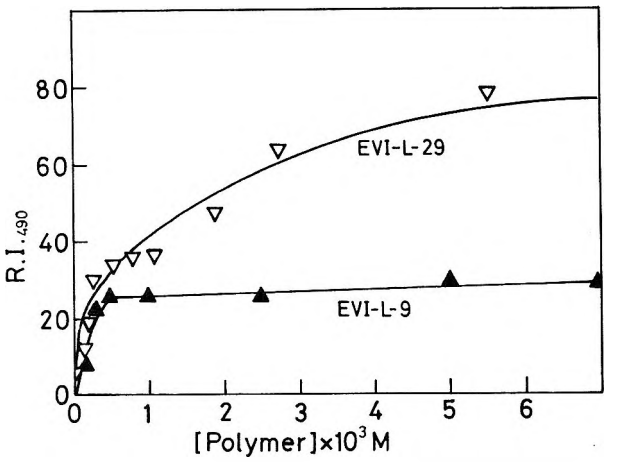


Figure 2. Relative intensity of fluorescent emission of 1-anilinonaphthalene-8-sulfonate (490 nm) plotted against the polymer concentration. [1-Anilinonaphthalene-8-sulfonate] = 1.0×10^{-4} M, room temperature.

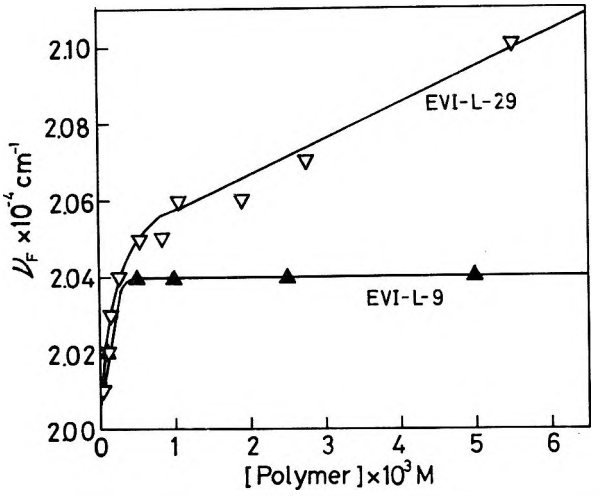


Figure 3. Wavenumber of maximum fluorescence of 1-anilinonaphthalene-8-sulfonate plotted against the polymer concentration. [1-Anilinonaphthalene-8-sulfonate] = 1.0×10^{-4} M, room temperature.

L-29, 4-VP-L-33, and 4-VP-L-22, and gradually reached saturation. Thus, these polymers can bind DCPI in the hydrophobic domain, causing the dissociation of DCPI. The binding constants (K_{DCPI}) evaluated based on the Benesi–Hildebrand equation[23] (correlation coefficient >0.99) are recorded in Table I.

Another useful method to monitor the formation of the hydrophobic region is the fluorescent emission. In Figure 2, the normalized relative intensity (R.I.) of 1-anilinonaphthalene-8-sulfonate (490 nm) is plotted as a function of the polymer concentration. The plots for EVI-L-9 rapidly saturated at [EVI-L-9] = ca. 5×10^{-4} M to give a plateau below R.I. 30. On the other hand, those for EVI-L-29 gradually increased up to R.I. 85 with increasing polysoap concentrations, indicating that the hydrophobicity is strengthened by the increased polysoap concentration. We also estimated the value for the conventional cationic micelle of hexadecyltrimethylammonium chloride (CTAC: 1.0×10^{-2} M) to be 32 under a similar condition.

Turner and Brand[24] have correlated the fluorescent emission maximum with the Kosower's Z value (a measure of the medium polarity[25])—the higher the wavenumber of maximum fluorescence (ν_F) of the adsorbed probe, the smaller the Z value. Figure 3 shows that the ν_F value reaches a constant value at a small concentration of EVI-L-9, whereas EVI-L-29

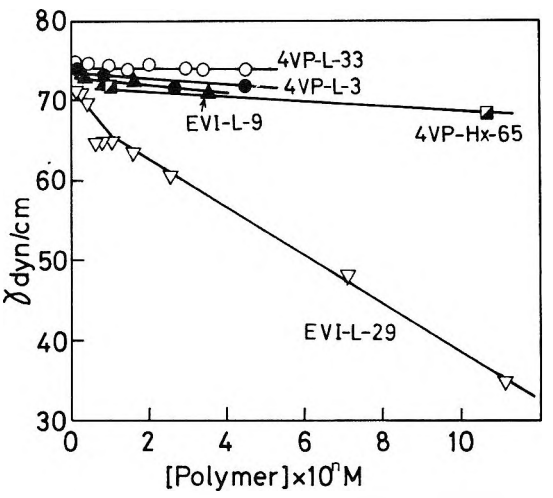


Figure 4. Surface tension at room temperature plotted against the polymer concentration: n = 4 for 4VP-L-33; n = 3 for other polymers.

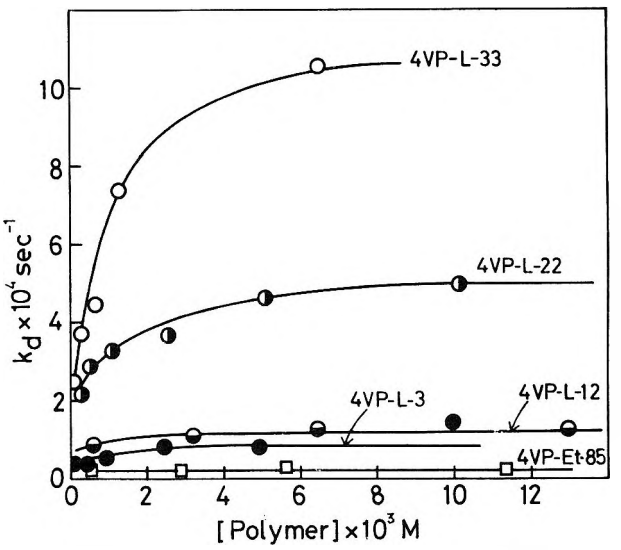


Figure 5. Decarboxylation rate plotted against the concentration of 4-VP-polymers: [I] = 1.35×10^{-4} M, pH 9.0 with 0.01 M borate, μ (KCl) = 0.013.

causes a significant shift to higher frequencies. The highest value (ν_F = 2.12×10^4 cm^{-1}) is close to those observed in ethanol (2.083×10^4 cm^{-1}) or in dioxane (2.118×10^4 cm^{-1}).[24]

Surface tension has been also utilized to demonstrate the aggregative behavior of surfactants. Polysoaps have been believed to be surface inactive, since they form the intramolecular micelle at very low concentrations.[5] As anticipated, EVI-L-9, 4-VP-L-33, 4-VP-L-3, and 4-VP-Hx-65 did not reduce the surface tension (γ) (Figure 4). The EVI-L-29 polymer, on the other hand, was surface active. The γ value plotted as a function of the polymer concentration gradually decreased, and was 36 dyn cm^{-1} at [EVI-L-29] = 1.1×10^{-2} M. This value is comparable to that of the micellar hexadecyltrimethylammonium bromide (CTAB).

Polysoap-Catalyzed Decarboxylation. The catalysis of decarboxylation of I by conventional cationic micelles features the sigmoidal dependence on the surfactant concentration[26,27]—the rate constant (k_d) is almost independent of the surfactant concentration below the cmc, while it rapidly rises with increasing concentration of surfactants above the cmc, and finally a plateau is obtained for surfactant concentrations well above the cmc. The catalysis by polysoaps with high lauryl group content showed a rapid increase in the rate constant at

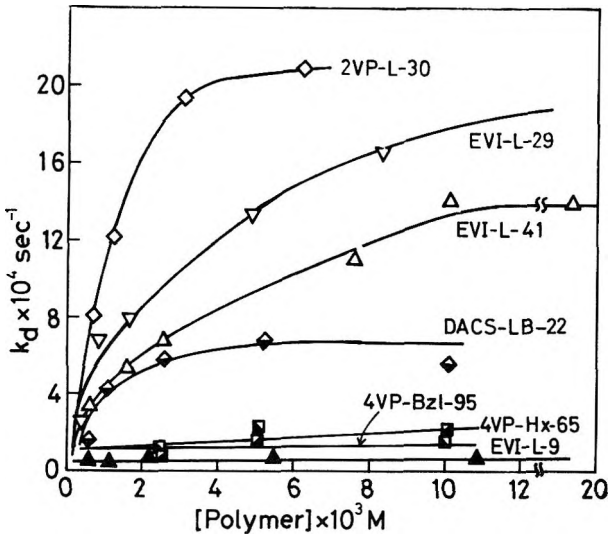


Figure 6. Decarboxylation rate plotted against the concentration of EVI and other polymers: [I] = 1.35×10^{-4} M, pH 9.0 with 0.01 M borate, μ (KCl) = 0.013.

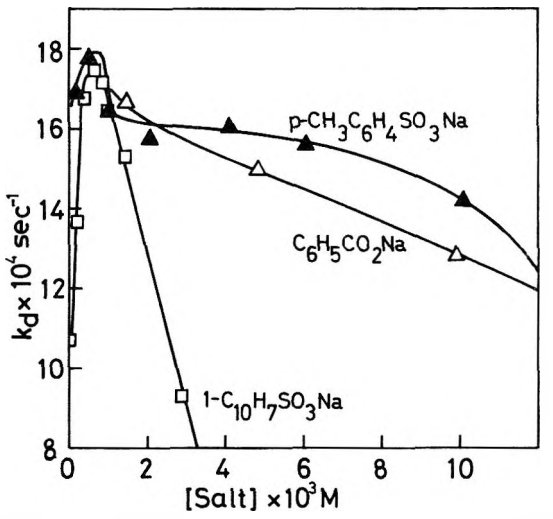


Figure 8. Effect of organic salts on the EVI-L-29 catalyzed decarboxylation: [I] = 1.35×10^{-4} M, pH 9.0 with 0.01 M borate, [EVI-L-29] = 8.4×10^{-3} M.

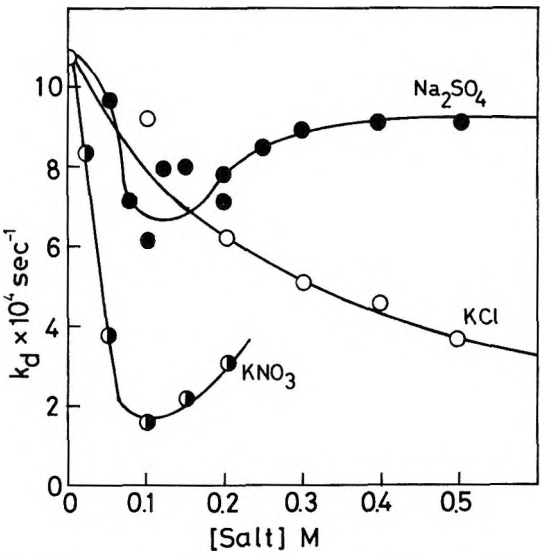


Figure 7. Effect of inorganic salts on the EVI-L-29 catalyzed decarboxylation: [I] = 1.35×10^{-4} M, pH 9.0 with 0.01 M borate, [EVI-L-29] = 8.4×10^{-3} M.

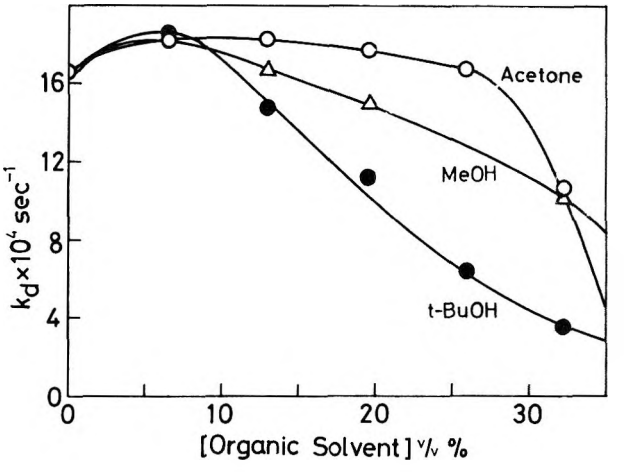


Figure 9. Effect of organic solvents on the EVI-L-29 catalyzed decarboxylation: [I] = 1.35×10^{-4} M, pH 9.0 with 0.01 M borate, [EVI-L-29] = 8.4×10^{-3} M.

very low concentrations of the polysoap, followed by gradual rate saturation (Figures 5 and 6). As anticipated from the spectral data, EVI-L-29 showed the maximal catalytic efficiency for the decarboxylation ($k_d = 2.10 \times 10^{-3}$ s^{-1} at μ = 0.004), which amounts to the rate augmentation of 350-fold compared with that in the nonmicellar system (6.0×10^{-6} s^{-1}). The catalytic efficiency of EVI-L-29 exceeds that of the CTAB micelle ($k_d = 3.10 \times 10^{-4}$ s^{-1} at [CTAB] = 3×10^{-3} M). Figures 5 and 6 indicate that 4-VP-L-33, 4-VP-L-30, DACS-LB-22, and EVI-L-41 also serve as efficient catalysts for the decarboxylation. It is worth emphasizing that these polysoaps all caused appreciable hypsochromic shifts for methyl orange and enhanced dissociation of DCPI. In contrast, less hydrophobic polysoaps such as 4-VP-L-3, 4-VP-Et-85, 4-VP-Bzl-95, and EVI-L-9, which hardly affected the spectra of methyl orange and DCPI, did not display significant catalysis. It is evident, therefore, that the decarboxylation is only accelerated by those polysoaps with hydrophobic regions as detected by the spectral shift studies.

Further studies of the polysoap-catalyzed decarboxylation was conducted with EVI-L-29, the most efficient catalyst among polysoaps tested herein. Figures 7 and 8 give the influence of added salts on the EVI-L-29 catalysis. The kinetic salt effect observed is complex, as in the case of the conventional cationic micelles.[26,27] Addition of inorganic, hydrophilic salts (KCl, KNO_3, Na_2SO_4) first retarded the reaction, but the rate increased at higher concentrations except for KCl. k_d might be also raised at the KCl concentration well above the concentration recorded in Figure 7. However, the EVI-L-29 solution became turbid at much higher KCl concentrations. Interestingly, low concentrations of organic salts (sulfonate and benzoate) appreciably enhanced the reaction rate, and rate maxima were observed. The maxima appeared where the concentration of the aromatic anions is close to that of the laurylated EVI unit.

Addition of organic solvents also affected the decarboxylation rate (Figure 9). In general, the reaction accelerated by hydrophobic environments is suppressed by addition of organic solvents. For decarboxylation of I this is not the case, however. Three solvents tested provided slight rate maxima at 5–10 vol/vol % of the solvent added. The influence was small below 20 vol/vol %, but the larger rate decreases were found above 20 vol/vol %.

Decarboxylation in Organic Solvents. The reaction in organic solvents was initiated by neutralizing the carboxylic acid with excess proton sponge [1,8-bis(dimethylamino)-naphthalene]. The water content was determined immediately after the reaction. The increase in the water concentration in

Table II. Decarboxylation Rates Adsorbed to the Polymer and the Association Constants[a]

Polymer	$k_d'' \times 10^3$, s^{-1}	K, M^{-1}	r
EVI-L-41	1.62	301	0.988
EVI-L-29	2.63	231	0.999
EVI-L-29[b]	2.86	991	0.994
EVI-L-29[c]	2.24	555	0.992
EVI-L-9	(0.04)		
2-VP-L-30	2.63	671	0.998
4-VP-L-33	1.01	2370	0.997
4-VP-L-22	0.460	3270	0.979
4-VP-L-12	(0.120)		
4-VP-L-3	(0.083)		
4-VP-Et-85	(0.021)		
4-VP-Hx-65	(0.210)		
4-VP-Bzl-95	(0.110)		
DACS-LB-22	0.643	1740	0.898
None	(0.006)		

[a] 30 °C, pH 9.0 with 0.01 M borate, μ (KCl) = 0.013, [EVI-L-29] = 5.0×10^{-3} M. [b] μ (KCl) = 0.004. [c] [*p*-Toluenesulfonate] = 5.0×10^{-4} M. Parenthesized data mean the decarboxylation rates at the highest polymer concentrations.

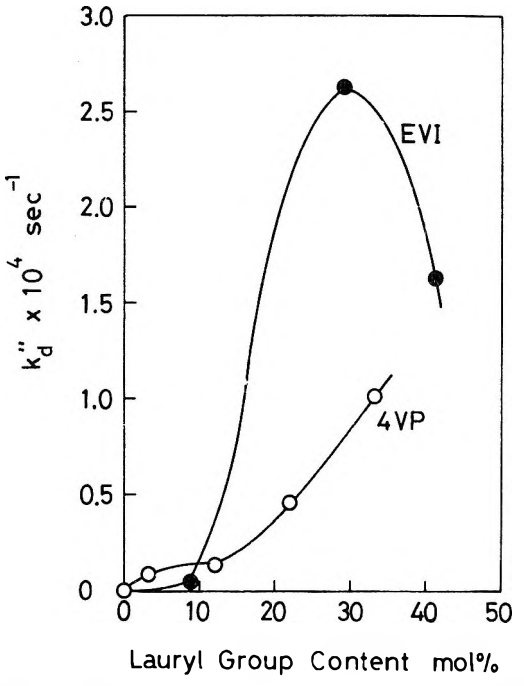


Figure 10. Decarboxylation rate of I adsorbed to the polymer plotted against the lauryl group content.

benzonitrile from 3 to 83 mM caused the rate decrease from 2.1 to 1.6 s^{-1}. The rate changes in benzene (H_2O: 6–20 mM) and in acetonitrile (H_2O: 16–125 mM) were smaller. Therefore, the decarboxylation rate is much less susceptible to minute amounts of water than the rate of bimolecular reactions involving oxyanionic nucleophiles.[14,15]

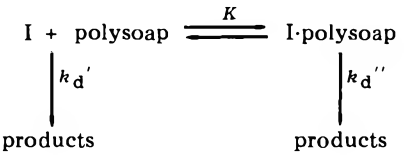
Discussion

The polysoap is generally believed not to possess the cmc unlike conventional micelles.[5] Instead, the transition from polyelectrolyte to polymer micelle is observed at 10–13 mol % of the lauryl-group content, where drastic reduction in viscosity and increase in solubilization ability occur.[5,6,9] The spectral studies also indicated this transition: polymers with more than 12 mol % of the lauryl group caused the micellelike spectral changes, while polymers with less lauryl groups hardly affected the spectrum of the adsorbed dye. Thus, the former polymers would be classified as polymer micelles and the latter as typical polyelectrolytes. The decarboxylation of I was catalyzed only by polymer micelles.

The absorption spectrum of methyl orange and the fluorescent emission of 1-anilinonaphthalene-8-sulfonate indicate that the hydrophobic environment of some polymer micelles is comparable to that of ethanol. In particular, aqueous EVI-L-29 showed the highest hydrophobic nature, despite its lower lauryl-group content than that of EVI-L-41. It is said that incorporation of excess lauryl groups stiffens the polymer chain and an expanded conformation results.[5] Table I shows that the smaller the intrinsic viscosity, the larger are the shifts of methyl orange and the K_{DCPI} value (EVI-L-29 > EVI-L-41 ≫ EVI-L-9). Therefore, the hydrophobicity of the polymer micelle is closely related to the conformational compactness of the polymer chain.

Plots of the rate constant against the polymer concentration (Figures 5 and 6) resemble those for spectral data (Figures 1–3), except that R.I. of the fluorescent emission increases at high polymer concentrations (Figure 3). Concentration–rate profiles in Figures 5 and 6 can be rationalized by the necessity of micellelike hydrophobic environments for the catalysis and by adsorption of a progressively greater fraction of the substrate into the polymer phase. The kinetic situation is expressed by Scheme I, where K is the equilibrium constant for

Scheme I



the association of substrate with polymer (= [I adsorbed]/[I][polymer]), k_d' is the decarboxylation rate constant in the nonpolymeric system, and k_d'' is that for the polymer-bound species. The following equation has been derived for [polymer] ≫ [I][28]

$$\frac{k_d'}{k_d - k_d'} = \frac{1}{qK\,[\text{polymer}]} + \frac{1}{q} \qquad (2)$$

where k_d is the rate constant obtained at a given polymer concentration and $q = (k_d''/k_d') - 1$. Excellent correlations (r = 0.98–0.99 except for DACS-LB-22; Table II) were found for this treatment. The decarboxylation rates of the polymer-bound substrate (k_d'', Table II) are parallel to the hydrophobicity evaluated by spectral studies (EVI-L-29 > EVI-L-41 ≫ EVI-L-9).

In Figure 10, k_d'' was plotted against lauryl-group contents of 4-VP and EVI polymers. Equation 2 could not be applied to polymers of low lauryl contents and, in these cases, rate constants observed at highest polymer concentrations were employed. Marked rate enhancements are found at ca. 15 mol % of the lauryl group content, which undoubtedly indicates the transition from polyelectrolyte to polymer micelle.

The correlation recognized between the decarboxylation rate and spectral data suggests that this reaction may serve as a kinetic probe to assess the hydrophobic environments of polysoaps. Figure 11 shows plots of log k_d'' against the wavenumber of the absorption maximum of methyl orange (ν_{MO}). For most polysoaps, log k_d'' is linearly correlated with ν_{MO} by eq 3 (solid line in Figure 11).

$$\log k_d'' = 1.03 \times 10^{-3}\,\nu_{MO} - 26.8 \qquad (3)$$

Plots for 4-VP-Hx-65 and 4-VP-Bzl-95 deviate to the upper side. These polysoaps would be able to provide the hydrophobic domain for the catalysis, but it is not sufficient for the spectral shift. On the other hand, polysoaps with large hy-

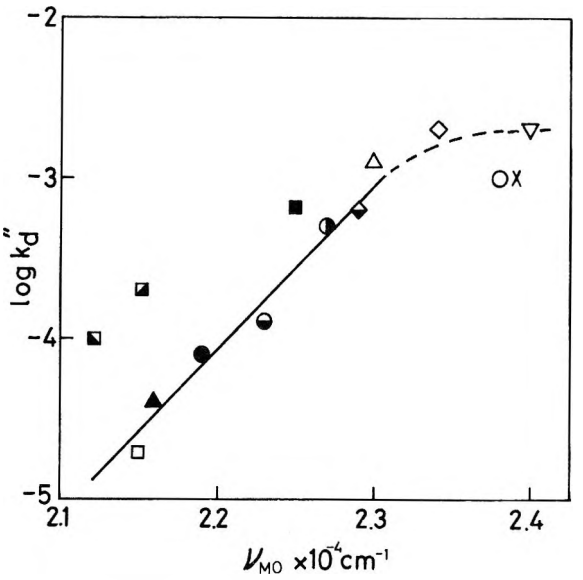


Figure 11. Correlation between log k_d'' and the frequency of absorption maximum of methyl orange: (△) EVI-L-41; (▽) EVI-L-29; (▲) EVI-L-9; (◇) 2-VP-L-30; (○) 4-VP-L-33; (◑) 4-VP-L-22; (◒) 4-VP-L-12; (●) 4-VP-L-3; (□) 4-VP-Et-85; (◪) 4-VP-Hx-65; (◨) 4-VP-Bzl-95; (◈) DACS-LB-22; (X) ethanol; (■) formamide.

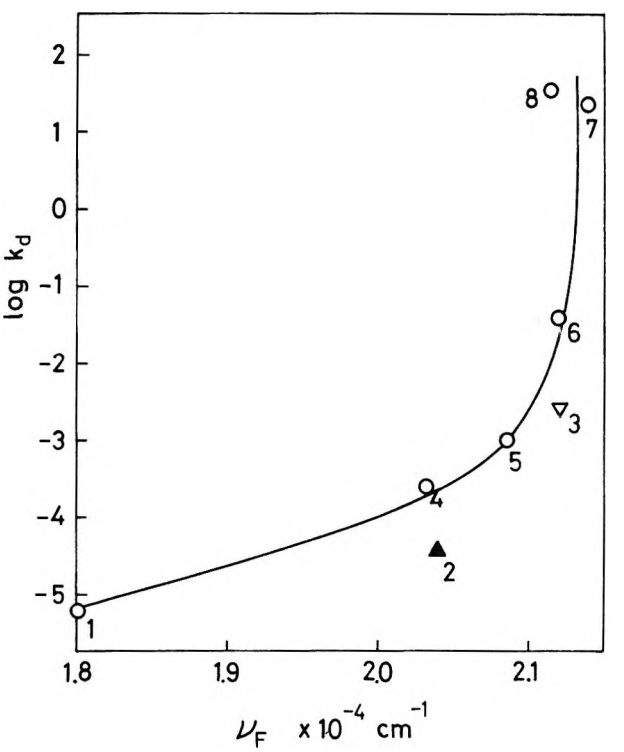


Figure 12. Correlation between log k_d and the frequency of fluorescent emission maximum of 1-anilinonaphthalene-8-sulfonate: (1) H_2O; (2) EVI-L-9; (3) EVI-L-29; (4) methanol; (5) ethanol; (6) dioxane; (7) acetone; (8) dimethylformamide. Plots for 4–8 are cited from ref 24 and 31.

drophobicity such as EVI-L-29 and 4VP-L-33 give plots deviated to the lower area. The polysoap catalysis may have an upper limit, though no saturation is observed for the methyl orange shift. The plots for ethanol ($\nu_{MO} = 2.39 \times 10^4$ cm^{-1}) and formamide ($\nu_{MO} = 2.25 \times 10^4$ cm^{-1}) were placed close to those for polysoaps.

Bovine serum albumin, a carrier protein, efficiently binds methyl orange and causes a hypsochromic shift.[18-20] Therefore, we expected that albumin also serves as catalyst for the decarboxylation. However, addition of bovine serum albumin (4×10^{-4} M) did not increase the decarboxylation rate.[29]

Now we discuss the origin of the rate enhancement. We previously pointed out that anionic nucleophiles are unusually activated by cationic micelles and that this is mainly caused by the formation of hydrophobic, desolvated ion pairs.[13-15] Very recently, Kemp and co-workers, who had reported for the first time (1970) decarboxylation of I to be remarkably solvent dependent,[30] claimed that the decarboxylation rate was influenced by hydrogen bonding of the carboxylate ion with protic solvents (inhibition), and the stabilization of the transition state in dipolar aprotic solvents (acceleration).[31,32] They argued that these factors are the essential conditions for the construction of practical enzymelike catalysts. Bunton and co-workers[25-27] claimed that the micellar catalysis of the decarboxylation of I is due to the action of the positive charge of the micelles for stabilizing the anionic transition state (II). On the other hand, Berezin and co-workers[33] emphasized the importance of dehydration of the carboxylate anion by the hydrophobic environment of micelles, and proposed that the micellar charges are utilized only for binding the reactant to the micelles.

The solvent effect on the decarboxylation of the carboxylate anion possesses contrasting behavior with the bimolecular nucleophilic reaction of some oxy anions: (1) the rate of the decarboxylation in benzene (4.8×10^{-3} s^{-1}) is not much different from that in formamide (7.4×10^{-4} s^{-1}),[31] whereas the nucleophilic attack of the hydroxamate anion toward *p*-nitrophenyl acetate is more than 10^6 times faster in benzene than in formamide;[15] (2) the decarboxylation is almost independent of the small variation of the water content in aprotic solvents, whereas the nucleophilic reaction involving oxy anionic nucleophiles is suppressed by extremely minute amounts of water.[14,15,32] Thus, it is implied that the decarboxylation involving an extensively delocalized transition state (II) is relatively insusceptible to desolvation (dehydration) as compared with the nucleophilic process. The transition state stabilization seems to play a heavier role in the decarboxylation.

The logarithm of the rate constant was plotted against the ν_F value, a measure of the medium polarity.[24] Figure 12 shows that plots for the polysoap-catalyzed reaction are placed close to those for methanol and ethanol, dipolar protic solvents. On the other hand, dipolar aprotic solvents such as acetone and dimethylformamide further accelerate the decarboxylation rate in spite of the similar ν_F values. This difference may be attributable to desolvation of the carboxylate anion.

Kinetic salt effects observed in the presence of EVI-L-29 are complicated. Generally, addition of electrolytes inhibits micellar catalyses. This inhibition was rationalized by assuming that a counterion competes with an ionic reactant for a site on the ionic micelle. However, Bunton and co-workers[26,27] noticed that the CTAB micelle-catalyzed decarboxylation of I is unexpectedly enhanced by some salts: small, hydrophilic anions enhance the rate at concentrations of 0–0.8 M, while hydrophobic anions such as aryl sulfonates, phosphates, and carboxylates increase the rate, giving maxima characteristic of each anion. They attributed their peculiar finding to the change in the micellar structure. In the polysoap system, the salt effect found for hydrophobic anions is similar to that found in the conventional micelle system (Figure 8), but addition of hydrophilic anions retarded the rate, and gave rate minima with KNO_3 and Na_2SO_4. These effects probably reflect the conformational change of polymer micelles. However, no simple explanation is apparent at present.

In conclusion, cationic polysoaps are found to serve as efficient catalysts for decarboxylation of I compared with the conventional cationic micelles. At the same time, the importance of the hydrophobic environment is substantiated through the correlation between the spectral and kinetic data.

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The Molecular Structure of Athabasca Asphaltene. Cleavage of the Carbon–Sulfur Bonds by Radical Ion Electron Transfer Reactions

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The molecular structure of Athabasca asphaltene from northeastern Alberta has been investigated. The large asphaltene molecules of mol wt 5920 were reduced by electron transfer from naphthalene radical anions produced in situ by treatment of naphthalene with potassium in tetrahydrofuran solution. The asphaltene anions were stabilized by octylation or protonation. From the number of octyl groups and potassium atoms consumed and the number average molecular weight of the treated asphaltene it was determined that the molecular weight on an octyl-free basis decreased tenfold during reduction. The extent of hydrogen bonding in the molecule was determined from the reduction in molecular weight upon silylation and diazomethane treatment to be one bond per molecule. It was also established that at least two-thirds of the oxygen is present in hydroxyl groups and some in carbonyl groups. The average aromatic carbon and aromatic hydrogen contents were determined to be 42 and 8%, respectively, by NMR spectroscopy. From the above results and those obtained in an auxiliary study of naphthalene anion reduction of simple model sulfur compounds, it is concluded that the Athabasca asphaltene has a sulfur polymeric framework in which the average carbon moieties, consisting of an alicyclic diaromatic structure with some alkyl substituents, are held together by sulfide linkages. It is shown experimentally that at least 65% of the sulfur is present in sulfide bonds, but other considerations suggest that the true figure is at least 90%. A solvent extraction scheme allowed some fractionation of the whole asphaltene. The 15% alcohol and acetone soluble fraction contains 40% of the oxygen present in the asphaltene molecule.

Asphaltene, the ubiquitous high molecular weight pentane insoluble fraction of petroleum, is a complex mixture of polycyclic aromatic molecules. In general, petroleum asphaltene is characterized by its high heteroatom content which in the case of the northeastern Alberta Athabasca asphaltene is in the range of sulfur 8–9%, oxygen 2–3%, and nitrogen ~1%. The chemical composition and molecular weight distribution show considerable variation with the source reservoir and depth, and the concentration may also vary from a few tenths of 1% in light crude oils to 25% in the Athabasca bitumen.

The molecular structure of asphaltene poses a challenge to the structural chemist and in spite of the numerous studies addressed to the problem the crucial question of whether asphaltene is a carbon polymer or a polymer in which the smaller carbon monomers are joined together by heteroatom linkages still remains unresolved. According to currently accepted notions the heteroatoms present in asphaltene are built into the ring systems of the molecules, which view, if correct, would favor a carbon polymer skeleton. A knowledge of the molecular structure would have practical and theoretical ramifications. It could have potential significance on the refining and upgrading processes of heavy crudes and bitumens, the production of bitumen from oil sands, and the possible commercial utilization of asphaltene and could also shed light on the mode of the formation of asphaltene and the diagenetic history of the source reservoir.

Most of the earlier studies reported in the literature on the molecular structure of asphaltene employed physical methods and the few chemical investigations which appeared were rather limited in scope. The most informative study is probably that published by Sawatzky and Montgomery[1] in which the molecular weight of Mildred Lake (northeastern Alberta) asphaltene was decreased from 6110 to 3547 by a single step reduction with lithium aluminum hydride and also by three successive reductions in ethylenediamine with a large excess of lithium. The decrease in molecular weight was attributed to cleavage of sulfide or ether bonds. More recently reduction

Table I. Average Molecular Weight of Asphaltene in Various Solvents

Solvent	Mol wt
Benzene	5920
CH_2Br_2	5480
CH_2Br_2 + dioxane	5500
Pyridine	5450

of coal with potassium and naphthalene followed by alkylation has been used for solubilization of coal.[2] Cleavage of ether linkages was thought to take place but solubilization was attributed mainly to the alkylation process.

In the present chemical approach to the structural elucidation of Athabasca asphaltene we have tried several mild oxidative and reductive degradative reactions of which the most suitable one was the treatment of asphaltene with potassium in tetrahydrofuran (THF) solution in the presence of naphthalene as an electron transfer agent. The C–S and C–O linkages are known to undergo cleavage reactions on electron transfer, RXR + e → RX^- + R·, while C–C bonds in general are resistant to this type of cleavage. This system appeared to be promising for the clarification of the role that the heteroatoms play in the polymeric skeleton. Cleavage of the C–X bond or removal of the heteroatom would not cause degradation of the polymer if the heteroatoms are part of the ring systems but degradation and an accompanying decrease in molecular weight would result if the sulfur and oxygen atoms were essential in holding together the polymeric framework of the asphaltene molecule.

The mechanism of C–S and C–O bond cleavages by electron transfer is not well understood. Consequently, parallel to the asphaltene studies, it was necessary to carry out some cursory auxiliary studies on simple model systems.

Experimental Section

1. Materials. The asphaltene was separated from the bitumen by the standard method of *n*-pentane precipitation.[3] Oil sand from Great Canadian Oil Sand Co. obtained through the courtesy of the Alberta Research Council was extracted with benzene and the bitumen was freed from the solvent by evaporation. A 1:1 mixture of the bitumen and benzene was diluted with 60 volumes of pentane and the precipitated asphaltene collected under nitrogen on a 10–20 μm porosity sintered glass funnel. The asphaltene was Soxhlet extracted for 24 h with pentane and dried. The yield of asphaltene averaged 16%. Anal. C, 80.27; H, 8.01; N, 1.21; S, 8.18; O, 2.50. Mol wt (by vapor pressure osmometry) 5920 ± 900, as the mean and standard deviation from seven measurements. These data give the molecular formula $C_{393}H_{472}N_5S_{15}O_9$.

THF was purified by distillation from potassium under nitrogen. The potassium, which had been cleaned by melting, was weighed quickly in the THF and used for the reaction.

Diazomethane was prepared from Diazald (Aldrich) according to the manufacturer's instructions. Lithium aluminum hydride solution was prepared by refluxing a large excess of commercial lithium aluminum hydride in dry THF, filtering through dried Celite, and concentrating the filtrate slightly. The concentration of hydride was determined by adding an aliquot to wet THF and measuring the volume of hydrogen evolved. Octyl iodide was used as received (over silver) from Terochem Laboratories, Edmonton. Recrystallized naphthalene (Anachemia) and hexamethyldisilazane (Eastman) were also used as such.

Quantitative GC analysis was performed on a Hewlett-Packard HP 5730A gas chromatograph with a 3380A integrator, using the internal standard method calibrated with a mixture of known weights of products. A 6 ft × 0.125 in. column of 3% OV-17 on Chromosorb W was used with a helium flow of 20 ml/min. A 12 ft × 0.125 in. column of 3% OV17 on Chromosorb W was used for determining the more volatile products. The oven was programmed from 75 to 270 °C at 8 °C/min.

Elemental analyses reported are the average of at least two determinations giving consistent results. In the case of the reduction and octylation experiment, the analysis is the average of several experiments each analyzed in duplicate.

The ir spectra were obtained as a 2% solution in ethanol-free chloroform using 0.5-mm NaCl cells.

The molecular weights were determined on a Mechrolab 301 vapor pressure osmometer at a concentration of 12–25 mg/ml. Benzil at various concentrations was used to calibrate the instrument. Benzene was used as solvent except where otherwise stated. Variation of the asphaltene molecular weight with solvent is shown in Table I.

2. Reduction and Octylation of Asphaltene and Model Compounds. Potassium (4 g, 0.10 g-atom) and naphthalene (0.30 g, 0.0024 mol) in 100 ml of dry THF were stirred under argon until the green-black color of the radical anion had developed. Asphaltene (4 g) or model sulfide (0.020 mol) was added and the mixture stirred for 168 h. The unreacted potassium was removed and either 24.01 g (0.100 mol) of octyl iodide or 25 ml of ethanol was added dropwise. Stirring was continued for 16 h for octylation and 2 h for protonation.

The products from the model reactions were extracted with ether and the ether solution dried over magnesium sulfate. An internal standard was added to an aliquot and the products determined by quantitative GC analysis.

The asphaltene reaction mixture was concentrated to about 50 ml, poured into 600 ml of 70% aqueous ethanol, and stirred for 2 h. The precipitated resinous product was redissolved in 50 ml of THF and precipitated again in the same manner. This procedure was repeated three or four times to ensure the complete removal of octyl iodide, inorganic salts, and naphthalene. Most of the dioctyl sulfide and alkylated naphthalene was also removed. The octylated product was pumped at 50 °C (1 mmHg) for 24 h. Analysis of the octylated product from the total asphaltene: C, 82.59; H, 11.02; N, 0.52; S, 2.88; O, 2.92. Analysis of the octylated product from the acetone insoluble asphaltene: C, 82.74; H, 11.02; N, 0.53; S, 2.35; O, 3.03. Part of the product was dissolved in THF, an internal standard was added, and the amount of dioctyl sulfide, dioctyl disulfide, hexadecane, and alkylated naphthalene remaining was determined by quantitative GC analysis. The total amount of all these by-products was about 7% of the purified product. The molecular weight of the octylated asphaltene was calculated from the experimental molecular weight M using the equation[4]

$$M = \frac{\Sigma W_n}{\Sigma(W_n/M_n)}$$

where W_n is the weight and M_n the molecular weight of the nth component.

The number of octyl groups/100C (n) is calculated from the hydrogen and carbon atoms added to the asphaltene by each octyl group.

$$\frac{120 + 17n}{100 + 8n} = \frac{H}{C} \text{ observed and } n = \frac{100\frac{H}{C} - 120}{17 - 8\frac{H}{C}}$$

It is assumed that the number of hydrogen atoms in the asphaltene part of the molecule, 120, does not change on octylation. The octyl free part of the octylated asphaltene is estimated by adding the molecular weight contributed by n octyl groups ($113n$) to the molecular weight of the asphaltene/100C (1500):

$$\text{Octyl free part} = \frac{1500}{1500 + 113n}$$

3. Treatment of Asphaltene with Reagents Capable of Blocking Hydroxyl Groups. A. Reactions with Diazomethane. Asphaltene (1.60 g), suspended in 50 ml of dry ether, was cooled in ice water. To this, a solution of 26.8 mol of diazomethane in 150 ml of ether was added. After 1 h stirring, the mixture was left to react for 72 h at 5 °C, and then allowed to stand at room temperature for 16 h. Unreacted diazomethane was removed by bubbling dry nitrogen gas through the solution. Ether was removed from the asphaltene sample by rotary evaporation. The methylated asphaltene was dried under vacuum for 24 h, yield 1.70 g (106.3% of substrate). Anal. C, 79.55; H, 8.08; N, 1.31; S, 7.79; O, 3.27.

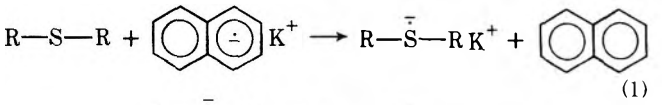
B. Reaction with Hexamethyldisilazane. Asphaltene (2.49 g) was refluxed for 4 h under nitrogen with 20 ml (0.095 mcl) of hexamethyldisilazane in 60 ml of dry THF. The reaction mixture was left for 24 h at room temperature and then the solvent and unreacted reagent were removed by distillation under vacuum. The dry residue showed some solubility in pentane, so no washing was possible. Instead, the product was dried under vacuum at 0.5 mmHg to constant weight, 2.82 g (113.3% of asphaltene). Anal. C, 80.49; H, 8.72; N, 1.87; S, 7.92; O, 1.87; ash, 4.05.

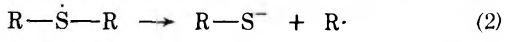
4. Determination of OH Groups by Hydrogen Evolution. In control experiments, 10 ml of 3.63 M lithium aluminum hydride in

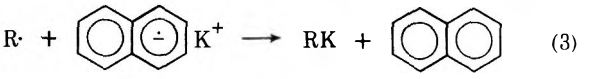
THF solution and 50 ml of dry THF were added to a flask connected to a gas buret. The pressure was equilibrated and 50 ml of THF added from a dropping funnel. The volume of hydrogen evolved was 21.4 ml. Similarly, a solution of 3.505 g of asphaltene in 50 ml of THF was added to 10 ml of 3.63 M lithium aluminum hydride in THF solution diluted with 50 ml of THF. The volume of hydrogen evolved was 115.6 ml; therefore, 3.505 g of asphaltene gives 115.6 − 21.4 = 94.2 ml of H_2 at 700.2 mmHg and 298.5 K which corresponds to 3.54 mmol. Now since 1 g of asphaltene contains 1.56 mg-atoms of O, then the amount of oxygen as OH is given by (3.54/3.505 ÷ 1.56) × 100 = 65%.

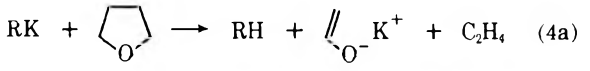
Results and Discussion

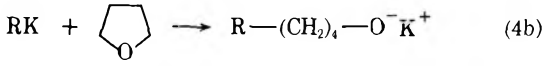
A. Reduction with Potassium in THF. The mechanism for reduction of an organic sulfide by electron transfer is not known, but by analogy with the reduction of halides[5,6] and on the basis of the nature of products observed, the following scheme appears to apply:


(1)

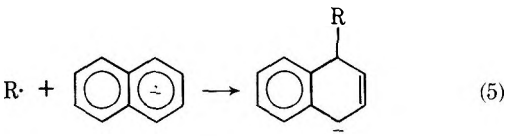

(2)

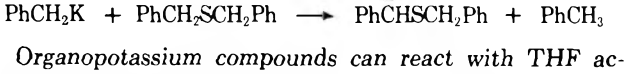

(3)


(4a)

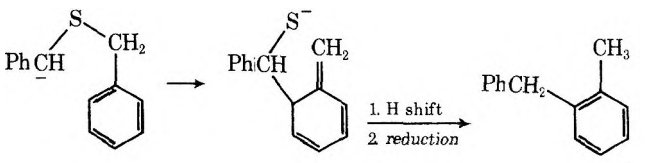

(4b)

In the absence of free-radical scavengers, reduction of the radical R· to R^-, step 3, is usually the fastest reaction of the radical. Dimerization of the radical does not compete, but addition of the radical to the naphthalene radical anion may:

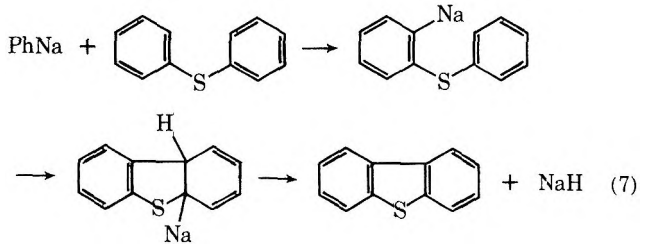

(5)



Organopotassium compounds can react with THF according to steps 4a and 4b. Simple organometallic compounds react with THF by proton exchange[7] but resonance-stabilized organometallic compounds such as diphenylmethyllithium react by nucleophilic ring opening (step 4b).[8] The organopotassium compounds generated in the reduction may also attack the starting material or products leading to side reactions. Known examples are[9,10]


(6)

1


(7)

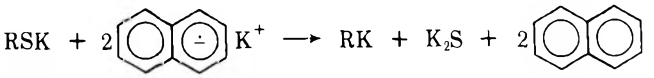
PhNa + PhSPh ⟶ PhPh + PhSNa (8)

The reactions 7 and 8 were carried out in benzene but a related reaction

$$Ph_2NK + PhK \rightarrow PhPh + PhNK_2$$

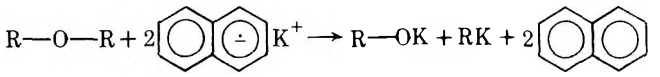
has been observed in THF.[11] Reactions 6–8 involve formation of a new carbon–carbon bond, and although carbon–sulfur bond cleavage and possibly desulfurization may occur, reduction in the gross molecular weight will be negligible.

Desulfurization during the reaction requires that the potassium thiolate produced in step 2 undergoes further reaction with potassium naphthalenide:

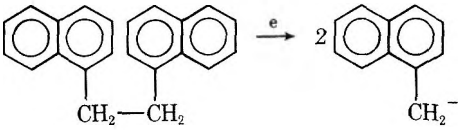


Even less is known about this reaction, but it probably proceeds via a series of steps analagous to 1–3 above.

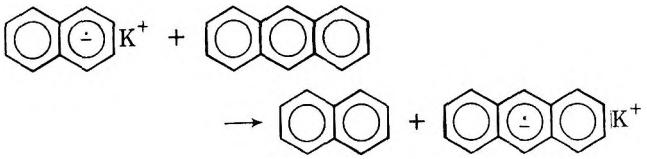
Other ways in which the asphaltene may react with potassium must also be considered. Cleavage of ethers may occur:[5]



In order for this reaction to take place, one of the groups R must be aryl, benzyl, or allyl; cleavage of dialkyl ethers occurs only under very vigorous conditions. Cleavage of carbon–carbon bonds has only been observed in some 1,2-polyarylethanes:[5]

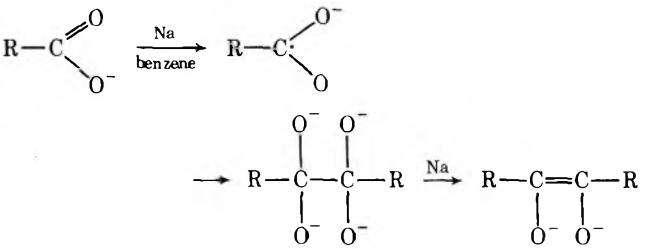


An important reaction will be transfer of an electron to polynuclear aromatic ring systems:



2

The resulting ions **2** are generally stable under the reaction conditions, giving dihydroaromatic compounds on workup. Transfer of electrons to other unsaturated groups may lead to more reactive radical ions which dimerize, as in the acyloin condensation



and the reductive dimerization of pyridine:[12]

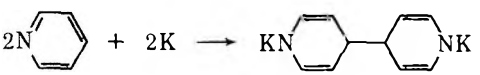
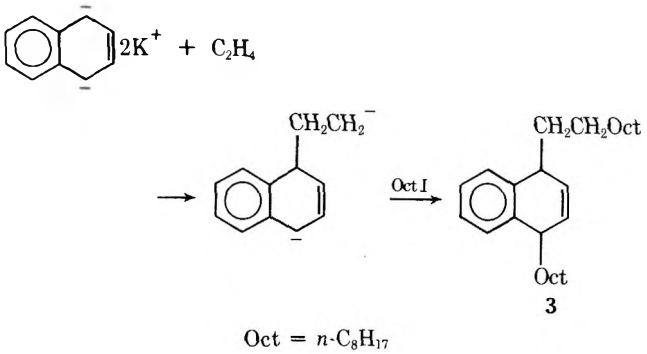


Table II. Reactions of Model Sulfur Compounds

Reactant	Products on protonation	Yield[a]	Products on octylation[b]	Yield[a]	Potassium consumed, g-atoms/mol
Diphenyl sulfide	Benzene	c	Benzene	91	2
	Benzenethiol	63	Phenyl octyl sulfide	96	
	Biphenyl	11	Biphenyl	16	
Dibenzyl sulfide	Toluene	72	Toluene	86	3
	1[d]	51	1[d]	11	
Dioctyl sulfide[e]	Octane	c			1
	Octanethiol	25			
	Dioctyl disulfide[f]	22			
	Dioctyl sulfide (recovered)	45			
Phenyl octyl sulfide	Benzenethiol	69			
	Octane	67			
Dibenzothiophene	Biphenyl	52	Biphenyl	62	5.4
2-Naphthalenethiol[g,h]	Dihydronaphthalene	36			
	Naphthalene	11			
	Tetralin	7			

[a] Moles of product per 100 mol of starting material. [b] Dioctyl sulfide was also produced when desulfurization occurred. [c] Not measured. [d] This product contained a small amount of dibenzyl by NMR. [e] This compound was reduced for 3 days only. [f] From oxidation of octanethiol on workup. [g] Reduction was by refluxing for 21 h with no naphthalene present. [h] About 15% of an unidentified by-product was formed, probably a dimer by GC retention time.

Since naphthalene is regenerated during the reduction in steps 1 and 3, we used less than stoichiometric amounts of naphthalene with respect to potassium. For most of the reactions, excess potassium was removed at the end of reduction and octyl iodide was added to convert the anions generated to their octyl derivatives. The reduced and octylated asphaltenes were more soluble and more stable than the reduced and protonated asphaltenes. To determine the products expected from the naphthalene used, a blank experiment was carried out in which naphthalene and excess potassium were stirred in THF and octyl iodide then added. The products as determined by GC–MS analysis were naphthalene (53% recovered), hexadecane (formed from octyl iodide), dioctyldihydronaphthalene (5%), and decycloctyldihydronaphthalene **3**[13] (5%) leaving 37% of the naphthalene unaccounted for. The product **3** is formed by the reaction[14]

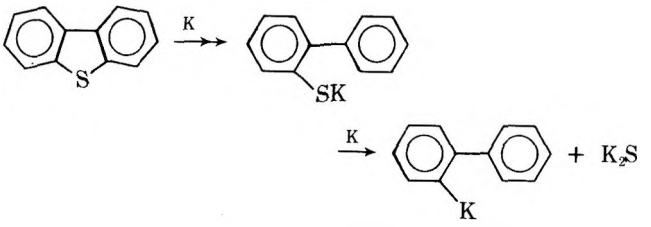


3

Oct = n-C_8H_{17}

The ethylene required is produced by decomposition of THF (as in step 4). It is reported that only the naphthalene dianion adds to ethylene; the radical anion is unreactive.[14] Formation of **3** demonstrates that the naphthalene dianion, a very strong base, is present in our reducing system in addition to the radical anion.

Reduction of several simple sulfides was carried out under the reaction conditions used for the asphaltene to assist in the interpretation of the asphaltene results and to evaluate the importance of the various side reactions discussed above. The results are compiled in Table II. Diphenyl sulfide and dibenzyl sulfide had been previously reduced with potassium in dimethoxyethane[9,15] in essential agreement with our results. From Table II it is seen that all types of organic sulfide will be cleaved by the reagent. However, desulfurization of the potassium thiolate occurs only for benzylthiolate, naphthalenethiolate, and biphenylthiolate. (Formation of biphenyl from dibenzothiophene implies that the reaction



has taken place.) Phenylthiolate and octylthiolate are not reduced. In the cases of diphenyl sulfide, dibenzyl sulfide, and probably naphthalenethiol some coupled products are observed. Although the yield of biphenyl from dibenzothiophene is only 52–62%, the by-product is not biphenylthiol since elemental analysis of the total product showed that 90% of the sulfur had been removed. The average molecular weight of the unidentified product is 2428 indicating that considerable polymerization has occurred. Elemental analysis showed that desulfurization of dibenzyl sulfide is complete.

Reduction of Asphaltene. The reduced and octylated asphaltene was analyzed and the number of octyl groups added were calculated from the change in the H/C ratio. It was found on average that 18 atoms of potassium were consumed and 9.4 octyl groups were added per 100 asphaltene carbon atoms.

The number of octyl groups added as calculated from the weight increase was 13.1. Part of the difference may be due to reaction with THF, step 4b. In support of this explanation, the oxygen content of the product was found to increase from 2.5 to 5.9 atoms/100C although some of this increase might be due to oxidation during workup. Additional weight increase might also be caused by reaction of benzyl potassium compounds with ethylene,[16] and by addition of the naphthalene radical anion to asphaltene radicals generated during reduction, step 5. The difference between the atoms of potassium consumed and the number of octyl groups added can be accounted for partly by formation of potassium sulfide (1.2 molecules/100C or 2.4 atoms of potassium) and potassium

Table III. Effect of Methylation and Silylation on the Molecular Weight and Solubility of Asphaltene

Asphaltene	Mol wt	% pentane soluble
Original	5920	1.5
Methylated	2950	13.6
Silylated	3200	15.3

naphthalenide (0.8 molecules of naphthalene/100C were used). The remaining 5.4 atoms of potassium must have been transferred from the asphaltene to THF by reaction 4a. On octylation the resulting acetaldehyde enolate would be expected to give decanal and/or octyl vinyl ether. These compounds should be extracted by the 70% aqueous ethanol washes, although they were not detected by GC–MS in either the extract or the product.

The experimental molecular weight for the reduced and octylated asphaltene was 930. After correction for the octyl groups and small amounts of impurities present, the average molecular weight of the asphaltene part of the product is calculated to be 580.

In order to elucidate the mechanism of this remarkable reduction in the average molecular weight of the asphaltene, we examined the possible role that intermolecular association may play in the aggregation of the original asphaltene molecules, thus influencing the molecular weight. The average molecular weight determined in 0.006 M benzene solution from seven samples of asphaltene was 5920 ± 900. This compares well with the value of 6110 obtained by Sawatzky and Montgomery,[1a] who showed that the molecular weight was independent of concentration below 0.004 M (higher concentrations were not measured). We measured the molecular weight of the asphaltene in various solvents of different polarity. The results presented in Table I indicate that the average molecular weight of asphaltene is not significantly affected by the solvent. The role of hydrogen bonding in molecular aggregation was next explored using diazomethane, which converts carboxylic and phenolic hydroxyl groups to methyl esters and methyl ethers, and hexamethyldisilazane, which converts most hydroxyl groups to silyl derivatives. The ir spectrum of the methylated asphaltene shows carbonyl absorption at 1730 cm^{-1} with a broad band at 1250–1300 cm^{-1} typical of the C–O–R stretching vibrations in both ethers and esters. The silylated asphaltene shows the absorption of trimethylsilyl ethers at 1250, 1200, and 850 cm^{-1}, and ^1H NMR absorption near δ 0. As seen from the data given in Table III, there was a significant reduction in molecular weight, from about 5920 to 3000, and a simultaneous increase in pentane solubility. The decrease in molecular weight by about one-half shows that both methylation and silylation block the sites responsible for molecular aggregation via hydrogen bonding and means that on average there is roughly one hydrogen bond present per asphaltene molecule.

The hydrogen bonding functionality could be phenolic or carboxylic hydroxyl. The ir spectrum of the original asphaltene shows neither hydroxyl nor carboxylic acid absorption under the conditions used. The immediate effervescence on addition of diazomethane and the absorption at 1730 cm^{-1} in the methylated asphaltene suggest the possibility of the presence of carboxylic acid groups.

The decrease in molecular weight on reduction might also be associated with the broad range of molecular weight distribution in the asphaltene, which is separated only on the basis of pentane insolubility. In particular it was thought that the asphaltene might contain some relatively low molecular weight compounds which were insoluble in pentane only on account of their high polarity, or were adsorbed strongly on the surface of the asphaltene. To remove any such compounds, the asphaltene was Soxhlet extracted successively with methanol, 98% ethanol, and acetone. The results of two experiments are summarized in Table IV and as seen from the data 86% of the asphaltene is insoluble in acetone. The only major change in the elemental composition is a decrease in the number of oxygen atoms/100C from 2.34 to 1.29. The alcohol and acetone fractions are correspondingly enriched in oxygen, and their ir spectra show carbonyl absorption at 1710 cm^{-1} which is not discernible in the spectrum of the whole asphaltene.

The molecular weight of the acetone insoluble asphaltene is about 9000. The molecular weight calculated for the combined fractions is about 4400, compared to 5920 for the whole asphaltene, which suggests that solvent separation breaks up some of the association. The acetone insoluble asphaltene from the second experiment (mol wt 9884) was silylated and the molecular weight decreased to 4062. Reduction and octylation of this acetone insoluble asphaltene decreased the octyl-free average molecular weight to 534 which is very close to the value of 580 obtained on reduction of the whole asphaltene.

From the above results it appears to be securely established that the average molecular weight of the whole asphaltene is decreased from 5920 to 580 on reduction, and the average molecular weight of the acetone insoluble asphaltene is reduced from 9884 to 534. The decrease in molecular weight corresponds to cleavage of 9.2 bonds per molecule in the whole asphaltene (2.09 bonds/100C) and to cleavage of 17.5 bonds per molecule in the acetone insoluble asphaltene (2.44 bonds/100C).

In order to determine how many of the bonds cleaved could be the carbon–oxygen bonds of ethers, the number of oxygen atoms present in hydroxyl groups was measured. The maximum number of ether oxygen atoms can then be found by subtraction. Two methods were found to be useful for measurement of the number of hydroxyl groups. The number of trimethylsilyl groups introduced on silylation of the asphaltene can be readily determined from the integration of the ^1H NMR spectrum. This method gave 1.5 silyl groups/100C for the whole asphaltene and 1.7/100C for the acetone insoluble asphaltene. From the increase in the H/C ratio the number of silyl groups introduced was found to be 1.8/100C for both samples. The whole asphaltene contains 2.34 oxygen atoms/100C so that 1.5/2.34 = 64% of the oxygen is present as hydroxyl groups, leaving 36% or 0.84 oxygen atoms/100C which may be in ether groups. Supporting evidence for this value came from the volume of hydrogen evolved on addition of the asphaltene to lithium aluminum hydride solution. This corresponds to 65 and 81% (two determinations) of the oxygen atoms being present as hydroxyl groups. Not all of the 36% of the oxygen atoms which are not hydroxyl need be in ether groups; some of this oxygen may be present as ketones, esters, or possibly amides. The 1.7 silyl groups/100C introduced on silylation of the acetone insoluble asphaltene account for slightly more than the total number of oxygen atoms (1.23/100C in this sample), so it appears that all the oxygen atoms in the acetone-insoluble asphaltene are present as hydroxyl groups. The amount of hydrogen evolved, 1.96 and 2.17 mmol/100C from duplicate runs, corresponds to a greater number of oxygen atoms than were actually present.

Since all of the oxygen atoms in the acetone insoluble asphaltene appear to be present as hydroxyl groups, none are present as ether groups, and all of the 2.44 bonds/100C which are cleaved on reduction must be carbon–sulfur bonds (where the sulfur atoms are not in a ring). The remaining 3.68 − 2.44 = 1.24 sulfur atoms may be in rings or may not have been reduced. Every coupling side reaction of the type discussed

Table IV. Extraction of Asphaltene with Polar Solvents

Solvent	Yield		H/100C		N/100C		S/100C		O/100C		Mol wt		Mol wt calcd from combined fractions	
	1[a]	2[a]	1	2[b]	1	2	1	2	1	2	1	2	1	2
Methanol	2.4	1.7	139	129	0.73	1.20	2.12	3.49	11.23	6.13	571	1108	3890	4891
98% ethanol	2.9	4.4	129		0.84		3.62		4.29		947			
Acetone	9.6	8.4	126	124	0.93	1.43	3.45	3.14	2.78	3.46	1167	1325		
Benzene	85.1	86.6	121	121	0.90	1.67	3.97	3.68	1.35	1.23	8363	9884		

[a] Data are given for two experiments, 1 and 2. [b] In experiment 2 the methanol and ethanol fractions were combined prior to analysis.

above reduces the apparent number of bond cleavages by one, which will lead to underestimation of the number of nonring carbon–sulfur bonds cleaved.

In the case of the whole asphaltene 0.84 oxygen atoms/100C may be in ether groups and could account for part of the 2.09 bonds/100C cleaved. However, it is not likely that all these oxygen atoms will be present as aryl ethers, some of the oxygen atoms may be in rings (e.g. benzofurans) and/or carbonyl groups, and comparison with the result from the acetone insoluble asphaltene suggests that cleavage of carbon–oxygen bonds is not important. Thus, the decrease in molecular weight of the total asphaltene on reduction is probably also due to the cleavage of nonring carbon–sulfur bonds.

Reductive Removal of Octyl Groups. Further treatment of the reduced and octylated asphaltene with potassium and naphthalene is expected to remove those octyl groups attached to sulfur and phenolic oxygen atoms. Octyl groups attached to carbon and alkyl oxygen atoms will be unaffected. Of the 9.4 octyl groups/100C added to the asphaltene after reduction and octylation, 6.0 remained after deoctylation so that 3.4 were attached to sulfur or phenolic oxygen atoms. The reduced and octylated asphaltene contained 2.7 sulfur atoms and 5.9 oxygen atoms per 100 asphaltene carbon atoms. Of the 3.4 octyl groups/100C removed, a total of 1.6 were found as octane (0.6), octanol (0.7), octanethiol (0.1), and hexadecane (0.2). The low value for octyl groups found, relative to those removed, may be caused by the difficulty of measurement, particularly for octane, and by the addition of octyl groups to naphthalene radical anion (reaction 5). Since all of the 2.7 sulfur atoms should have been octylated according to the model reactions, $3.4 - 2.7 = 0.7$ octyl groups must have been removed from phenolic oxygen atoms.

Decrease in Sulfur Content. Reduction of the asphaltene with potassium and naphthalene removed 30% of the sulfur, decreasing the number of sulfur atoms/100C by 1.1, from 3.8 to 2.7. On the basis of the model reactions this result implies that 1.1 sulfur atoms/100C in the asphaltene are attached to polyaryl or benzyl groups and 2.7 attached to phenyl or alkyl groups. The desulfurization of the acetone insoluble asphaltene was slightly higher, 39%, so of the 3.7 sulfur atoms/100C, 1.4 were attached to polyaryl or benzyl groups and 2.3 to phenyl or alkyl groups.

Role of Naphthalene. Sternberg et al.[2] used naphthalene in the reaction of coal with potassium because neither coal nor potassium have appreciable solubility in THF. Asphaltene is soluble in THF and almost certainly contains some polycyclic aromatic nuclei which can act as electron transfer agents. Therefore, it seemed possible that asphaltene would react with potassium without naphthalene present. When the asphaltene was treated with potassium in the absence of naphthalene, but otherwise under the same conditions as before, reaction did take place but the decrease in molecular weight and sulfur content was lower than that found when naphthalene was present. These results are shown in Table V for both the whole asphaltene and the acetone insoluble asphaltene. since the

Table V. Comparison of the Reduction of Asphaltene by Potassium with and without Naphthalene Present

Reaction	Mol wt of product (octyl free)	% of sulfur removed	Octyl groups added per 100C
Whole asphaltene with naphthalene present	580	30	9.4
Whole asphaltene without naphthalene present	1900	18	5.9
Acetone insoluble asphaltene with naphthalene present	530	33	9.3
Acetone insoluble asphaltene without naphthalene present	1600	15	5.9

extent of desulfurization and the number of octyl groups added are lower without naphthalene present, the simplest explanation for the smaller decrease in molecular weight is that the reaction is slower, i.e., fewer bonds are cleaved, because the concentration of reducing agent in solution is lower without added naphthalene. It may also be that the radicals generated during the reduction are less efficiently reduced when the concentration of reducing agent is lower so that addition of the radical to another asphaltene molecule (polymerization) competes with reduction of the radical.

B. Derivation of an Average Molecular Structure for the Asphaltene. The experimental evidence that the asphaltene can be readily cleaved by reduction into relatively small molecules requires reevaluation of some asphaltene structures suggested in the literature. One of the problems in determining a reasonable average structure for the asphaltene has been the difficulty in obtaining a value for the proportion of aromatic carbon. Methods adequate for lower boiling petroleum fractions based on density and refractive index correlations, are not fully satisfactory for large molecules relatively rich in heteroatoms. We have determined the ^{13}C NMR spectrum of the asphaltene in order to assess the proportion of aromatic carbon more directly. Combination of this value with the degree of unsaturation, determined by the H/C atomic ratio, and the percent of hydrogen atoms which are attached to aromatic rings (from the ^{1}H NMR spectrum) makes it possible to propose a structure for the average asphaltene molecule, although assumptions must still be made.

The ^{13}C NMR Spectrum of the Asphaltene. There are two problems in obtaining ^{13}C NMR spectra in which the peak areas correspond quantitatively to the number of carbon atoms.

Firstly, it is general practice to run the spectra with broad-band proton decoupling. This increases the signal intensity but the intensity enhancement is variable for different kinds of carbon. In the present case this problem was avoided by running the spectra with proton coupling and compen-

Table VI. Double Bond Equivalents per Carbon Atom (DBE/C) and the Ratio of Non-Ring-Junction to Ring Junction Carbon Atoms (C_4/C_5) for Some Aromatic Compounds

Compd	DBE/C	C_4/C_5
Benzene	0.67	∞
Naphthalene	0.70	4.00
Anthracene	0.71	2.50
Tetracene	0.72	2.00
Pyrene	0.75	1.67
Coronene	0.79	1.00
Ovalene	0.81	0.78
Graphite (C_∞)	1.00	0

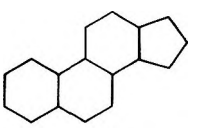
sating for the loss of intensity by using the maximum amount of sample. The second more difficult problem is that some carbon atoms, particularly those without attached protons, have very long relaxation times T_1, as high as 100 s. This means that the carbons are not completely relaxed between pulses. The time required for virtually complete relaxation is $5T_1$ s, and the practical limit for pulse repetition is 1 s or less, owing to the cost and availability of machine time. For the asphaltene this problem was solved by reducing the T_1's by three mechanisms: (1) dipole–dipole relaxation induced by the high viscosity of the solution;[17,18] (2) the application of a relatively low magnetic field, 15.08 MHz, since relaxation times are lower for a given correlation time at lower fields;[19] and (3) the use of a paramagnetic reagent, chromium acetylacetonate, to cause relaxation by spin–spin coupling. This reagent has been shown to reduce the relaxation time for an unprotonated carbon atom in cholesteryl chloride from 4.3 to 0.23 s.[18] Complete relaxation in the asphaltene sample was demonstrated experimentally by increasing the time between pulses from about 0.7 s used initially, to 1 s. No change in the relative signal intensities occurred. Under these conditions, using a concentrated sample containing chromium acetylacetonate, running the spectrum with proton coupling, low field strength, 1 s repetition time, and 90° pulses, the proportion of aromatic carbon was found to be 42%. The spectrum shows two broad peaks for the aliphatic and aromatic carbons with well-defined steps in the electronic integration curve. The aromatic peak occurred between 100 and 160 ppm from tetramethylsilane, centered at 135 ppm, and the aliphatic peak occurred between 0 and 60 ppm, centered at 30 ppm. The proportion of aromatic carbon in the acetone insoluble asphaltene was found to be slightly lower at 35%.

The proportion of hydrogen atoms which are attached to aromatic rings was found from the conventional ^1H NMR spectrum to be 8% for both the total asphaltene and the acetone insoluble asphaltene. The aromatic peak occurred between δ 5.8 and 8.5 and the saturated peak between δ 0.1 and 4.5. The H/C ratio is 1.2 for both fractions. It follows that of the 120 hydrogen atoms/100C 0.08 × 120 = 10 are attached to aromatic carbon atoms. Therefore, the fraction of substituted aromatic carbon atoms, including ring junctions, is 32/42 = 0.76.

Structural Analysis of the Average Asphaltene Molecule. The degree of unsaturation or number of double bond equivalents (DBE) of a molecule is given by the formula DBE = $(2N_C + 2 - N_H)/2$ where N_C is the number of carbon atoms and N_H the number of hydrogen atoms. For the asphaltene there are 120 hydrogen atoms/100C, so that DBE/100C = (200 + 2 − 120)/2 = 41.

There are 42 aromatic carbon atoms/100C and each aromatic carbon atom contributes about 0.72 double bond equivalents (vide infra). Therefore, the 42 aromatic carbon atoms contribute 42 × 0.72 = 30 DBE leaving 41 − 30 = 11 DBE to be contributed by the alicyclic carbon atoms. If it takes an average of four alicyclic carbon atoms to contribute one degree of unsaturation (as a ring), then the proportion of alicyclic carbon is 11 × 4 = 44%. This leaves 100 − 42 − 44 = 14% of paraffinic carbon atoms.

This analysis required assumptions to be made about the number of double bond equivalents per aromatic carbon atom and per alicyclic carbon atom. This data, determined by inspection of the structures, is given for a number of simple aromatic and alicyclic compounds in Tables VI and VII.



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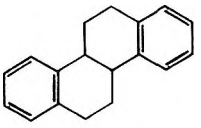

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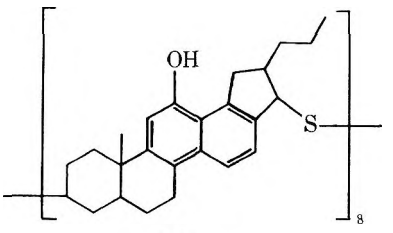
It can be seen that the DBE/aromatic carbon atom and alicyclic carbon atoms/alicyclic DBE used above (0.72 and 4) are middle of the range. Another reason for the use of 0.72 for the DBE/aromatic carbon atom is that the corresponding C_4/C_5 ratio is the minimum value of the range given by the Montgomery–Boyd analysis.[20] The value for alicyclic carbon atoms/alicyclic DBE cannot be higher than 5.3 or the number of paraffinic carbon atoms becomes negative. Values much lower than four seem unlikely because then the alicyclic proportion of the molecule must consist entirely of a very restricted range of structures, for example, it is unlikely that the asphaltene consists entirely of fluorene units joined together. Also, the alicyclic protons of fluorene absorb at δ 4 where the asphaltene shows virtually no absorption. However, a value of 3 for the number of alicyclic carbon atoms/alicyclic DBE is not unreasonable. This would reduce the number of alicyclic carbon atoms to 33% and increase the number of paraffinic carbon atoms to 25%. Greater accuracy cannot be expected without a means of measuring the number of alicyclic or paraffinic carbon atoms directly.

These qualitative estimates are useful in the construction of reasonable model structures for the average asphaltene molecule. The molecular formula of the average asphaltene molecule, after allowing for hydrogen bonding, is $C_{200}H_{240}N_2S_7O_4$ (mol wt 3000). Dividing by 8, which corresponds to cleavage of the polymer at all the sulfur atoms, gives a monomer unit with empirical formula $C_{25}H_{30}SX$, where X is the combined nitrogen and oxygen atoms. A molecule approximately consistent with the carbon and hydrogen distribution given above is



% aromatic carbon = $\frac{10}{25}$ = 40% (obsd 42%)

% aromatic hydrogen = $\frac{3}{30}$ = 10% (obsd 8%)

H/C = 1.2 (obsd 1.2)

aromatic DBE/aromatic carbon atom = $\frac{7}{10}$ = 0.70

alicyclic carbon atoms/alicyclic DBE = $\frac{11}{3}$ = 3.67

proportion of substituted aromatic carbon atoms = $\frac{7}{10}$ = 0.70

% alicyclic carbon atoms = $\frac{11}{25}$ = 44%

% paraffinic carbon atoms = $\frac{4}{25}$ = 16%

Since 64% of the oxygen atoms are present as hydroxyl groups, there is one hydroxyl group for every three of the monomer units shown. Of course a considerable variety of ring and substituent arrangements are possible and an enormous variety of structures will actually be present, leading to the average values given above. The degree of homogeneity of the hydrocarbon framework is not known. We can only assume that it is mainly derived from triterpenes.

The acetone insoluble asphaltene has slightly lower aromaticity, 35%. The carbon distribution, 35% aromatic, 64% alicyclic, and only 1% paraffinic, is obtained assuming that the DBE/aromatic carbon atom is 0.72 and that the alicyclic carbon atoms/alicyclic DBE ratio is 4. If the latter ratio is only 3, then the distribution becomes 35% aromatic carbon, 48% alicyclic carbon, and 17% paraffinic carbon.

This type of analysis was first attempted by Montgomery and Boyd[20] 15 years ago, prior to the availability of NMR, but a brief discussion seems appropriate. Their method involved correlating the number of various types of carbon atom with molar volume (mv) and molar refraction (mr) in a number of model compounds. The mv and mr of the asphaltene are then used to derive the number of each type of carbon atom in the asphaltene molecule. The carbon atoms were divided into five types: C_1, paraffinic carbon atoms; C_2, non-ring-junction alicyclic carbon atoms, including substituted ones; C_3, ring junction alicyclic carbon atoms, including substituted ones; C_4, non-ring-junction aromatic carbon atoms, including substituted ones; and C_5, ring junction aromatic carbon atoms. With five unknowns three more equations are required. One is available from the carbon balance, $C_1 + C_2 + C_3 + C_4 + C_5 = \Sigma C$. The next one used was $C_4 + C_5 = C_a$, the total number of aromatic carbon atoms. For lower molecular weight petroleum fractions, methods were available for estimating C_a, but these methods were not applicable to the asphaltene. Therefore this relation was essentially replaced by the condition that the number of carbon atoms C_1–C_5 all be greater than zero, which left a range of possible values instead of a unique solution. Finally, Montgomery and Boyd used the relation $2C_1 + 2C_2 + C_3 + C_4 = \Sigma H$ which follows from the definitions of these groups.

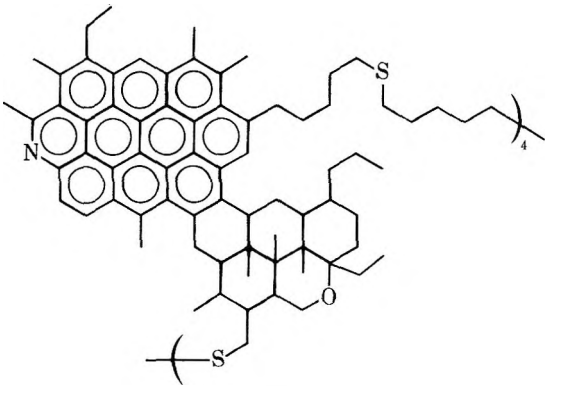
Employing this method, Sawatzky, Boyd, and Montgomery[1b] reported the following values for the Athabasca asphaltene: C_1, 33.8–34.2%; C_2, 0–6.5%; C_3, 10.3–0%; C_4, 45.2–41.2%; C_5, 11.2–18.0%, with the percent aromatic carbon ($C_4 + C_5$), 56.1–59.2%. (It should be noted that their asphaltene was prepared by extracting the oil sand with pentane and then with benzene.) In view of the limited amount of data and the rather crude analytical techniques available at the time, this analysis yielded surprisingly good results. In particular, the degree of condensation of the aromatic rings agrees with our results. The somewhat high value derived for the percent aromatic carbon results in correspondingly low values for the percent alicyclic carbon. The original classification did not distinguish between ring junction carbon atoms and carbon atoms linking aromatic rings (as in biphenyl). The latter were designated C_7, and the following distribution, applicable only when $C_3 = 0$, was calculated: C_1, 38.8%; C_2, 22.0%; C_4, 41.3%; C_5, 10.02%; C_7, 7.7%. Other work on density ring number correlations has been reported recently.[21]

Another structural analysis of the Athabasca asphaltene was attempted by Speight.[22] In this method the saturated ^1H NMR peak was dissected into areas attributed to benzylic, alicyclic, chain methylene, and chain methyl groups. The number of non-ring-junction aromatic carbon atoms is then the number of aromatic hydrogen atoms plus half the number of benzylic hydrogen atoms. The total number of aromatic carbon atoms is obtained by subtracting the saturated carbon atoms from the total carbon atoms. The number of saturated carbon atoms was calculated by dividing the estimated number of benzylic, alicyclic, and chain methylene hydrogen atoms by 2, and the chain methyl hydrogen atoms by 3. The ratio of non-ring-junction to ring junction aromatic carbon atoms (C_4/C_5 in the Montgomery–Boyd analysis) obtained in this way is 0.67, much lower than any value in the range of the Montgomery–Boyd analysis.[20] The low C_4/C_5 value corresponds to a highly condensed aromatic structure such as naphthoovalene. Determination of the number of each type of carbon atom from the number of hydrogen atoms is difficult because an assumption must be made about the extent of substitution of the carbon atoms. The saturated proton peak in our spectrum shows too much overlap to be resolved as suggested by Speight. Estimation of the relative number of alicyclic and chain methylene hydrogen atoms is particularly uncertain.

Table VII. The Number of Alicyclic Carbon Atoms per Alicyclic Double Bond Equivalent in Various Compounds

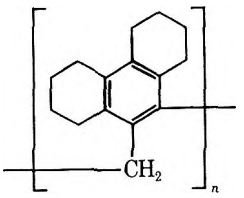
Compd	Alicyclic carbon/ alicyclic DBE
Cyclohexane	6
Cyclopentane	5
Decalin	5
4	4.25
Tetralin	4
5	3
9,10-Dihydroanthracene	2
Fluorene	1
Diamond (C_∞)	1

The percent aromaticity has also been determined by Yen and co-workers[23] from the intensity of the γ and (002) bands in the x-ray spectrum. Unfortunately these bands overlap substantially and considerable speculative curve resolving is necessary. The percent aromaticity reported for the Athabasca asphaltene was 31%,[24] slightly lower than the 42% we find from the ^{13}C NMR spectrum. Yen[25] recently proposed the following average structure for the Lagunillas asphaltene.



This asphaltene has an H/C ratio of 1.12, and 41% aromaticity as determined by the x-ray method. The highly condensed aromatic and alicyclic ring system in Yen's structure, with the lower H/C ratio and higher aromaticity, results in a small proportion of alicyclic carbon atoms. However, it should be noted that the value of F/C_A,[26] which determines the degree of ring condensation, is based on the assumption of a rectangular aromatic sheet, and also depends critically on the number of rings per carbon atom, which is determined from a density–ring number correlation.[27] The difficulties with these correlations have been discussed by Montgomery and Boyd[20] and by Yen.[27] In addition, the number of rings per carbon atom obtained from the density correlation is the total number of rings, whereas the number required for calculating

F/C_A is the number of aromatic rings. Use of the value for the number of rings obtained from densimetric analysis in the calculation of F/C_A implies the assumption that there are no alicyclic rings. This difficulty becomes very apparent in the analysis[24] of the octahydrophenanthrene–formaldehyde copolymer, e.g.



In calculating F/C_A a value of C/R[28] = 15 (i.e., R = 1) is used. Densimetric analysis should give R = 3 which would lead to an unreasonably high value of F/C_A.

It seems that an aromatic–alicyclic–paraffinic division of the carbon atoms is the most that can be expected. Combination of the aromatic–aliphatic NMR peak areas with molar volume and molar refraction correlations might provide a narrower classification.

Conclusions

In the present study it has been clearly established that Athabasca asphaltene is a sulfur polymer in which the average carbon moieties consisting of alicyclic diaromatic structures with some alkyl substituents are held together by sulfide linkages. Since most asphaltenes are rich in sulfur[29] irrespective of origin, it is probable that they also possess a sulfur polymer framework.

In the vast Athabasca oil sand formation of northeastern Alberta the concentration of asphaltene varies between 16 and 25% of the raw bitumen. In light of the molecular structure of the asphaltene, the high sulfur content of the bitumen cannot be construed upon as evidence for an old geological age or a significant geothermal history of the formation. The asphaltene probably arose from the interaction of microbiologically produced sulfur with the primary lighter crude oil, a process which can occur under mild conditions.

Further work is in progress.

Acknowledgments. The authors are grateful to the National Research Council for financial support and to Mr. Cleve Murray for technical assistance. It is also a pleasure to express our appreciation to Dr. D. S. Montgomery for many stimulating discussions on oil sand chemistry.

Registry No.—Naphthalene dianion, 23013-60-7; methanol, 67-56-1; ethanol, 64-17-5; acetone, 67-64-1; benzene, 71-43-2; potassium, 7440-09-7; naphthalene, 91-20-3; naphthalene radical anion, 34509-91-6; dibromomethane, 74-95-3; dioxane, 505-22-6; pyridine, 110-86-1.

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Carbon Acids. 12. Acidifying Effects of Phenyl Substituents

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Results of the replacement of one or two hydrogen atoms in CH_3EWG carbon acids (EWG = CH_3SO, CN, $PhSO_2$, CH_3CO, F_3CSO_2, and the like) by phenyl on equilibrium acidities in Me_2SO are reported. The progressive decrease in phenyl acidifying effects with a progressive increase in acidity of the CH_3EWG parent acids is interpreted as a resonance saturation effect. The acidifying effects of phenyl on $PhCH_2EWG$, 9,10-dihydroanthracene, and xanthene are found to be severely attenuated by steric inhibition of resonance. Similar effects were observed on substitution of a second Ph group into $PhCH_2EWG$ to give Ph_2CHEWG. The ratios of resonance to polar contributions to the acidifying effect of Ph were estimated by (a) removing the resonance contribution through steric inhibition of resonance and (b) by using the Me_3N^+ group as a model for polar effects. The first method indicated a ratio of 4:1, the second a ratio of 4.6:1 to 6.6:1 depending on the nature of EWG. The resonance to polar ratio for phenyl was found to be larger than that for PhCO (or CH_3CO), which, in turn, is much larger than that for NO_2, CN, or $PhSO_2$.

α-Phenyl substitution has been shown to increase the equilibrium acidities of a variety of parent carbon acids in a number of different solvent systems. Some of these data are summarized in Table I in terms of ΔpK units (the increase in acidity relative to that of the parent acid). It will be observed that the effects range from a few negative values to positive values as high as 4.4, and that ΔpK values in solvents as different as benzene, cyclohexylamine (CHA), dimethyl sulfoxide (Me_2SO), and Me_2SO–H_2O sometimes agree surprisingly well. We have pointed out previously that agreement of this kind between acidities in solvents of low dielectric constant (C_6H_6, CHA, etc.) and high dielectric constant (Me_2SO, Me_2SO–H_2O, etc.) occurs only, however, when the compounds and the reference indicators have similar structures.[2]

There is also an abundance of kinetic evidence to show that α-phenyl substitution increases the acidity of a hydrogen atom attached to carbon. Estimates of equilibrium acidities have often been made on the basis of such data. For example, from relative rates of lithium or cesium cyclohexylamide catalyzed tritium exchange rates in CHA, the relative "pK" of toluene in CHA has been placed at 41, and that of methane at a value higher by 5–8 pK units.[3,4]

Using equilibrium and kinetic acidity data of this type as a basis, molecular orbital calculations point to a pK for methane from 3 to 10 units higher than that of toluene.[5,6] Results of extrapolations from equilibrium acidities in Me_2SO show, however, that the difference in pK between toluene and methane is much greater than indicated by these estimates. (In Me_2SO toluene has a pK of ca. 44 and methane has a minimum pK of ca. 60.)[7]

The data in the present paper demonstrate that, in the absence of steric effects, α-phenyl substitution increases the acidity of parent acids to a much greater extent than suggested by the earlier data (Table I). The increases observed vary from 4.4 to 10.6 pK units, depending on the pK of the parent acid (Table II).

Results and Discussion

Comparison with Data in Other Solvents. Table II presents the pK's of a number of parent acids and their α-phenyl derivatives measured in Me_2SO by the method described previously.[2] Table II also shows the increase in acidity (change to lower pK values) caused by α-phenyl substitution, relative to a hydrogen atom in methane carbon acids (ΔpK_H) and relative to a methyl group in ethane carbon acids (ΔpK_{Me}). Comparison of the ΔpK's in Table II with those in Table I shows that the α-phenyl effects are generally much larger for the parent acids that we have examined in Me_2SO than for those reported in other solvent systems. In fact, the *smallest* ΔpK recorded in Table II for an unhindered system (4.4) is as large as any previously recorded in solution, and the largest ΔpK recorded in Table II (10.6) is 6.2 pK units larger than any previously observed. In many instances the smaller effects recorded in Table I are caused by steric inhibition of resonance in the carbanion, which prevent the phenyl group from exerting its maximum effect. Such steric effects are minimized for substitution of phenyl for a hydrogen atom in methane carbon acids, CH_3EWG, or for a methyl group in ethane carbon acids, $MeCH_2EWG$. For three carbon acids of this type for which comparable data are available (acetophenone, fluorene, and nitromethane) the effects in Me_2SO of substituting phenyl for hydrogen are somewhat larger than in other solvents.

For acetophenone α-Ph substitution increases the acidity in Me_2SO by 7.2 pK units (Table II) as compared to only 3.2 pK units in diglyme (Table I). Evidently in diglyme the ion pair (or ion aggregate), $M^+[C_6H_5COCH_2]^-$, is stabilized relative to the ion pair (or ion aggregate), $M^+[C_6H_5COCHPh]^-$, causing the equilibrium

$$M^+[C_6H_5COCHPh]^- + C_6H_5COCH_3 \rightleftarrows M^+[C_6H_5COCH_2]^- + C_6H_5COCH_2Ph$$

to shift to the right so as to partially compensate for the delocalizing ability of the phenyl group.[2]

For fluorene the phenyl effect is only ca. 0.6 pK units greater in Me_2SO than in benzene or CHA. This good agreement is apparently a consequence of the similarity of the stabilities of the two hydrocarbon ion pairs, $M^+[In]^-$ and $M^+[In']^-$, that are being balanced against one another in benzene or CHA.[2] (In^- and In'^- are highly delocalized indicator anions.)

For nitromethane the phenyl effect in Me_2SO is 1.6 units greater than that in water. This is not due to differences in stability of salt aggregates since ion association effects are absent in these solvents of high dielectric constant.[2] The larger ΔpK in Me_2SO in this instance can probably be attributed mainly to a relatively higher negative charge density on carbon in the nitronate ion, $PhCH{=}NO_2^-$, in Me_2SO than in water caused by the weak H-bond donor properties of Me_2SO. It is also possible that Me_2SO may be better than water at stabilizing the negative charge delocalized to the phenyl group in the nitronate ion.[8]

Comparison of Phenyl Effects in the Gas Phase and in Solution. The effect of phenyl substitution on the acidity of

Table I. Effect of α-Phenyl Substitution on Equilibrium Acidities of Carbon Acids

Parent acid[a]	ΔpK[b] C_6H_6[c]	CHA[d]	Me_2SO–HOH	Me_2SO[e]
Nitromethane			3.6[f]	
7*H*-Dibenzo[c,*g*]fluorene			1.2[g]	
13*H*-Dibenzo[*a*,*i*]fluorene			0.5[g]	
Fluorene	4.3	4.4	3.8[h]	4.4
Acetophenone	3.2[i]			
Phenylacetophenone	−0.2[i]			
Xanthene	0.3		3.2[h]	
9,9-Dimethyl-9,10-dihydroanthracene		1.8		
5*H*-Dibenzo[*a*,*d*]cycloheptadiene		−0.4		
Diphenylmethane	2.8	2.0	1.7[h]	2.0

[a] The acidities decrease as one proceeds down the table. [b] The (statistically corrected) increase in acidity caused by α-phenyl substitution. [c] W. K. McEwen, *J. Am. Chem. Soc.*, **58**, 1124 (1936). [d] A. Streitwieser, Jr., J. R. Murdoch, G. Häfelinger, and C. J. Chang, *ibid.*, **95**, 4248 (1973). [e] Data of E. C. Steiner and C. D. Ritchie given in "Solute-Solvent Interactions", J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 4, Table 4-2. [f] In water; from data compiled by A. T. Nielsen, "The Chemistry of Nitro and Nitroso Groups", H. Feuer, Ed., Wiley-Interscience, New York, N.Y., 1969, Chapter 7, Table 5. [g] H. Fischer and D. Rewicki, *Prog. Org. Chem.*, **7**, 116 (1968). [h] K. Bowden and A. F. Cockerill, *J. Chem. Soc. B*, 173 (1970). [i] In diglyme: H. D. Zook, W. L. Kelly, and I. Y. Posey, *J. Org. Chem.*, **33**, 3477 (1968).

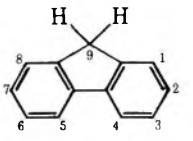
methane carbon acids can be discussed in terms of the equilibrium

$$PhCH_2EWG + CH_2EWG^- \rightleftharpoons PhCHEWG^- + CH_3EWG$$

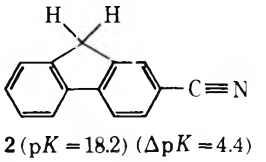
Although the relative stabilities of the undissociated acids, $PhCH_2EWG$ and CH_3EWG, will surely be of importance, it seems likely that the position of equilibrium will be determined primarily by the relative stabilities of the anions, CH_2EWG^- and $PhCHEWG^-$. The anions are stabilized by a combination of resonance and polar effects. Molecular orbital calculations indicate that the benzyl anion has a resonance energy of 0.72 β,[9] which is equivalent to a minimum resonance energy of 13 kcal/mol. Gas-phase acidity data indicate that substitution of a phenyl group into methane may increase the stability of the anion by as much as 33 kcal/mol.[10] Phenyl effects on the gas-phase acidities of the methane carbon acids, acetone and acetonitrile, are much smaller, however, being comparable in magnitude to those shown in Table II. In fact, in view of the linear relationship with near unit slope between acidities in the gas phase and in Me_2SO for two series of compounds, (a) CH_3CN, $PhCH_2CN$, $CNCH_2CN$, and (b) CH_3COCH_3, CH_3COPh, $PhCH_2COCH_3$, $PhCOCH_2COCH_3$, $CH_3COCH_2COCH_3$,[11] it would appear that the size of the phenyl effects for the methane carbon aicds, CH_3EWG, may approach those observed in the gas phase.

Effects of Methyl Substitution. Comparison of the p*K*'s of the parent methane carbon acids, HCH_2EWG, and ethane carbon acids, $MeCH_2EWG$, in Table II shows that substitution of a methyl group for a hydrogen atom causes a small increase in acidity for CH_3NO_2 and CH_3COPh (0.7 and 0.5 p*K* units, respectively), a small decrease in acidity for CH_3COCH_3 (0.3 p*K* unit), and a sizable decrease in acidity for the sulfone carbon acids, CH_3SO_2Ph, and $CH_3SO_2CF_3$ (1.7 and 1.4 p*K* units). The acidity of CH_3CH_2CN is too high to permit accurate measurement by our method, but it is definitely a weaker acid than CH_3CN. Judging from the fact that substitution of a methyl group for an α-hydrogen atom in $PhCH_2CN$ or $H_2C(CN)_2$ causes a decrease in acidity of slightly over 1 p*K* unit in each instance, a p*K* of 32.5 seems reasonable for $MeCH_2CN$.[12] (A detailed discussion of these methyl effects will be given in a later paper.)

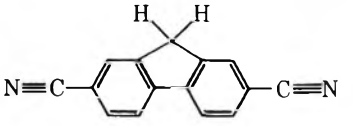
Saturation of the Phenyl Effect. The carbon acids in Table II are arranged in order of increasing acidity, the strongest acid, nitromethane, being 18.2 p*K* units stronger than the weakest acid, dimethyl sulfoxide.[2] The most striking feature of Table II is the progressive decrease in the size of the acid-strengthening effect of the phenyl group (ΔpK_H or ΔpK_{Me}) as we proceed down the series from the weakest parent acid to the strongest CH_3EWG or $MeCH_2EWG$ parent acid. In a previous paper in this series we showed that a strong electron-withdrawing group (EWG) such as CN caused a large (4.4 unit) increase when substituted for a hydrogen atom in the 2 position of the fluorene nucleus (**1**), but that when a



1 (p*K* = 22.6)



2 (p*K* = 18.2) (Δp*K* = 4.4)



3 (p*K* = 14.6) (Δp*K* = 3.6)

second CN group was substituted into an equivalent position in the other benzene ring, the 7 position, the acidifying effect was smaller (3.6 p*K* units).[13] It was suggested that the first cyano group decreases the charge density at the acidic site in the anion by charge delocalization, and that the stabilizing effect of substituting a second cyano group is less than that of the first because of this delocalizing effect. This was termed a *resonance saturation effect*. For our present purpose we can define a resonance saturation effect as the extent to which depletion of the negative charge at a given site in a carbanion by resonance causes an attenuation in the stabilizing (or destabilizing) effect of a group when substituted into that ion.

We believe that the resonance saturation effect is a general phenomenon in chemistry,[13] and that this is the primary reason for the decreasing acidifying effect of the phenyl group observed in Table II with increasing parent acid acidity. In other words, the stronger the parent acid, the greater the delocalization of the negative charge in the anion, the smaller the charge density in the anion on the carbon atom to which the phenyl group is attached, and the greater the resonance saturation effect. The operation of the saturation effect is shown graphically in Figure 1, where the p*K* of the parent methane carbon acids is plotted against ΔpK_H (Table II). [A similar plot is obtained for p*K* of $MeCH_2EWG$ vs. p*K* ($MeCH_2EWG$) − p*K* ($PhCH_2EWG$).] Examination of Figure 1 shows that the points for the "planar" EWG's (CN, $COCH_3$, COPh, and NO_2) and the "tetrahedral" EWG's ($SOCH_3$, SO_2CH_3, SO_2Ph, and SO_2CF_3) appear to fall on separate lines. The fall-off is much steeper for the "planar" EWG's (ΔpK_H decreases by ca. 5 p*K* units for a 14 p*K* increase in acidity for the former vs. ca. 2 p*K* units for a 17 p*K* unit increase in acidity for the latter). The fall-off for the "planar" EWG's is also somewhat greater than for substitution of CN into the 2 and 7 positions of fluorene (**1**–**3**), where a fall-off of only 0.8 p*K* unit was observed for an increase in parent acid acidity of 3.6 units (i.e., a fall-off of ca. 3 for a 14 p*K* unit increase in parent acid acidity). This is understandable since in the fluorene system the resonance saturation effect must operate through a benzene ring whereas in Table II the substituent

Table II. Effect on the Acidities in Me_2SO for Carbon Acids of Repacing a Hydrogen Atom or a Methyl Group by a Phenyl Group

Registry no.	Parent acid	pK^a	pK-(α-Ph)^b	$\Delta pK_H{}^c$	Registry no.	Parent acid ^{b}	pK	$\Delta pK_{Me}{}^f$
67-68-5	CH_3SOCH_3	35.1	29.1	6.5				
75-05-8	CH_3CN	31.3	21.9	9.6	107-12-0	$MeCH_2CN^d$	~32.5^d	10.6
67-71-0	$CH_3SO_2CH_3$	31.1	25.6	5.8	597-35-3	$(MeCH_2)_2SO_2$	~32.8^e	7.2
120-12-7	9,10-Dihydroanthracene	30.1	28.8	1.6				
92-83-1	Xanthene	30.0	27.9	2.4				
3112-85-4	CH_3SO_2Ph	29.0	23.4	5.8	599-70-2	$MeCH_2SO_2Ph$	31.0	7.6
67-64-1	CH_3COCH_3	26.5	19.8	7.2	96-22-0	$(MeCH_2)_2C{=}O$	27.1	7.3
98-86-2	CH_3COPh	24.7	17.7	7.2	93-55-0	$MeCH_2COPh$	24.4016.7	
421-82-9	$CH_3SO_2CF_3$	18.8	14.6	4.4	13003-57-1	$MeCH_2SO_2CF_3$	20.4	5.8
75-52-5	CH_3NO_2	17.2	12.2	5.2	79-24-3	$MeCH_2NO_2$	16.7	4.5

^{a} See ref 2. ^{b} Runs against at least two indicators; standard deviations within runs are generally less than ±0.05 pK unit. ^{c} Statistically corrected for the number of acidic protons. ^{d} Decomposition occurs; pK estimated from the Me effects observed with $PhCH_2CN$ or $CH_2(CN)_2$ as parent acids. ^{e} Assuming that the Me effect is the same as observed with CH_3SO_2Ph or $CH_3SO_2CF_3$ as parent acids. ^{f} ΔpK_{Me} = pK(MeCH$_2$EWG) − pK(PhCH$_2$EWG).

is being introduced directly at the acidic site.[14] The latter effect is larger, but also more complex. In the fluorene system (1–3) complications arising from solvent effects, steric effects, and polar effects are eliminated by the remote positioning of the substituents,[13] but in replacing H in CH_3EWG or Me in $MeCH_2EWG$ by Ph all of these factors must be considered.

Replacement of a hydrogen atom in a methane carbon acid, CH_3EWG, by a phenyl group will certainly lead to changes in solvation, particularly in the anion. A methyl group is a much better model in this respect than a hydrogen atom, but is far from ideal. A methyl group is also a better model for phenyl with regard to steric effects. Steric effects between phenyl and EWG are not expected to be large. They should be minimal for anions containing the (linear) cyano group, and will probably be somewhat greater in anions containing the (tetrahedral) sulfone group. The phenyl group must, of course, have its π system parallel to the lobes of the p orbital of the carbanion for maximum overlap. In this respect its steric demands differ from those of methyl, and we can expect some variation in steric effects for the different $PhCHEWG^-$ anions. The variations in solvation and steric factors, just discussed, are likely to be small and relatively constant; therefore, they will probably not interfere seriously with the determination of the size of the resonance saturation effect in the $PhCH_2EWG$ series. The major factor affecting the size of the fall-off factor is likely to be the ratio of resonance to polar contributions for each EWG; steric interactions between Ph and EWG in the anion need to be considered as a possible perturbing factor, particularly in the more crowded systems. Since the ratio of resonance to polar contributions will be different for each EWG, we cannot expect the resonance saturation effect to be directly proportional to the parent acid acidity but instead to vary with the change in the ratio of resonance to polar effects.

The rather steep fall-off in the size of the Ph effect from CH_3CN to CH_3COPh (or CH_3COCH_3) to CH_3NO_2 (the "planar" functions) brought out in Figure 1 is believed to be due principally to the increasing degree to which the negative charge in the anion is located on the heteroatom, rather than on carbon. In $CH_2{=}C{=}N^-$ the negative charge on the nitrogen atom is less than that on the (more electronegative) oxygen atom in $CH_2{=}C(O^-)Ph$, and in $CH_2{=}NO_2^-$ the charge is distributed over *two* oxygen atoms. The result is a progressive decrease in the charge density on carbon, and a progressively smaller Ph effect. Some steric interactions may be present, but these are believed to be of minor consequence.

The sulfoxide and sulfone functions differ from the "planar" functions in that the carbanion carbon is linked to a large

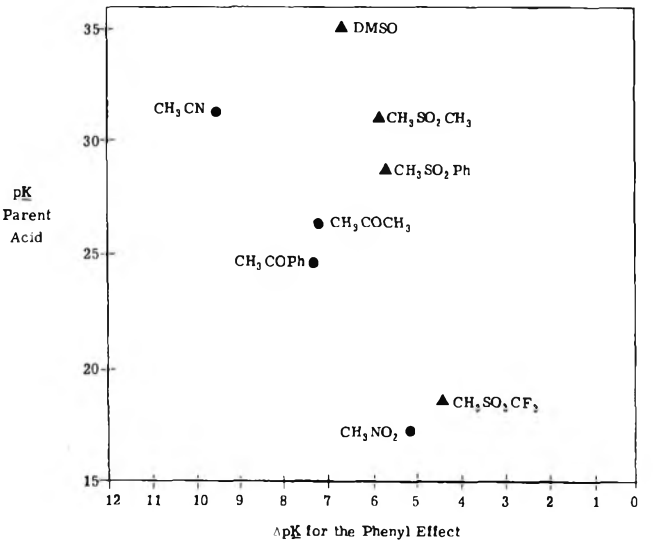


Figure 1. Plot of the acidifying effect of the phenyl group vs. the pK of the parent acid: ●, for "planar" functions; ▲, for "tetrahedral" functions.

second-row element, which is attached to four ligands in a tetrahedral arrangement. Steric effects are obviously important in these systems, but may be relatively constant. This would explain why the points for the "planar" and "tetrahedral" functions fall on different lines. The relatively small fall-off factor for the "tetrahedral" functions, as compared to the "planar" functions (Figure 1) suggests that the ratio of contribution of resonance to polar effects for these functions is relatively small, and that the marked increase in acidity on replacing Ph in SO_2Ph by CF_3 is primarily the result of an increase in the polar factor.

Steric Inhibition of Resonance in Phenyl-Substituted Carbanions. Since the phenyl group has a relatively small polar effect (σ_I = 0.10[15]), one would anticipate that the large acidifying effects observed (Table II) must be due primarily to its ability to stabilize the anion by delocalization of charge. This view is supported by the relatively small acidifying effects of phenyl that have been observed in molecules where steric crowding prevents effective overlap between the p orbital of the carbanion and the π system of the phenyl group (Table I). Taking examples of this kind from our work in Me_2SO, we find that 9-phenyl-9,10-dihydroanthracene and 9-phenylxanthene are only 1.6 and 2.4 pK units more acidic, respectively, than their parents, 9,10-dihydroanthracene and xanthene (Table

Table III. Effect of a Second α-Phenyl Group on the Acidities of Carbon Acids in Me_2SO

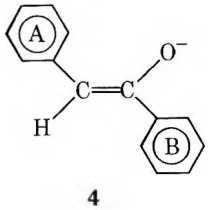
Registry no.	Diphenyl-substituted acid	pK^a	ΔpK^b
86-29-3	Diphenylacetonitrile	17.5	4.7
1733-63-7	α,α-Diphenylacetophenone	18.7$_5$	−0.8
102-04-5	α,α-Diphenylacetone	19.4	0.7
7476-11-1	α,α,α′,α′-Tetraphenylacetone	17.6$_5$	
5433-76-1	Diphenylmethyl phenyl sulfone	22.3	1.4
19552-15-9	Bis(diphenylmethyl) sulfone	21.9	
5427-04-3	Diphenylmethyl phenyl sulfoxide	24.5	3.0
519-73-3	Triphenylmethane	30.6	2.0

[a] Absolute values, not statistically corrected. [b] Relative to the monophenyl carbon acid (Table II); statistically corrected.

II). Examination of scalar molecular models shows that the π systems of the phenyl groups in the anions derived from 9-phenyl-9,10-dihydroanthracene or 9-phenylxanthene are at almost right angles to the p orbital of the carbanion. Delocalization of the charge into the phenyl groups in these anions must be strongly inhibited, and the acidifying effect of the phenyl groups must be largely polar in nature.

The acidifying effect of phenyl groups is also attenuated by steric effects when phenyl is substituted for hydrogen in carbon acids of the type $PhCH_2EWG$ (Table III).

Examination of Table III shows that the phenyl substituent produces its largest acidifying effect (ΔpK = 4.7) when substituted for a hydrogen atom in phenylacetonitrile, i.e., $PhCH_2CN \rightarrow Ph_2CHCN$. (This is not surprising since the cyano group has the smallest steric demands of any of the common EWG functions.) Nevertheless, this acidifying effect is 4.9 pK units smaller than that produced by replacing a hydrogen atom in CH_3CN by a phenyl substituent (Table II). Most of the smaller effect must be due to a resonance saturation effect since the $PhCH_2CN$ parent acid has a 9.6 pK unit greater acidity than the CH_3CN parent acid. Using Figure 1 as a guide, we find that the 4.7 pK unit acidifying effect is only about 1.5 pK units smaller than expected. Examination of scalar molecular models indicates that the phenyl groups in the Ph_2CHCN^- anion need to be twisted only slightly out of the plane of C=C=N$^-$ function. On the other hand, twisting of the phenyl groups must be severe in the Ph_3C^-, Ph_2CSOPh^-, $Ph_2CSO_2Ph^-$, $Ph_2CHSO_2CPh_2^-$, $Ph_2CHCOCPh_2^-$, $CH_3COCPh_2^-$, and Ph_2CCOPh^- anions.[16] The greatest steric inhibition of resonance is encountered with the ketones. Examination of scalar molecular models shows that the phenyl groups in the enolate ion from acetophenone can achieve the *trans*-stilbene conformation, 4, with minimal steric interference. Phenyl ring A is close to the enolate oxygen atom, but hindrance can be relieved by bending the bond to the hydrogen atom. Substitution of the hydrogen atom on the C=C bond in 4 by phenyl can be achieved only by bringing



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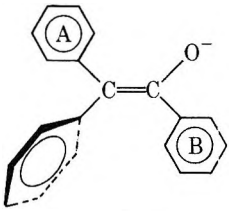


5

the phenyl group in at right angles to the plane of the enolate ion, as in **5**. Even so, it is necessary to twist ring A. The loss in resonance energy from twisting ring A (or rings A and B) is evidently greater than the polar effect contributed by the third phenyl ring, and ΔpK is *negative* (Table III). (α,α-Diphenylacetophenone has also been found to be less acidic than α-phenylacetophenone in diglyme.[19]) A ΔpK of ca. 5 is predicted for the phenyl effect on α-phenylacetophenone from the correlation of ΔpK with parent acid acidities in Figure 1. A loss in resonance energy corresponding to 5 pK units is 6.8 kcal/mol, which is comparable to the difference in resonance energies between *trans*- and *cis*-stilbenes, as it should be.

Resonance vs. Polar Contributions for the Anion-Stabilizing Effect of Phenyl. In an earlier section we saw that substitution of a phenyl group for a hydrogen atom in the 9 position of 9,10-dihydroanthracene or xanthene caused only a 1.6 and 2.4 pK unit increase in acidity, whereas an increase of 8 or 9 pK units might have been anticipated for such weak parent acids in the absence of steric effects. If we assume that these small acidity increases provide an estimate of the size of the polar effect, it would appear that the ratio of resonance to polar contributions for phenyl is about 4:1.

The ratio of resonance to polar contributions for G in GCH_2EWG systems, where EWG is CN, SO_2Ph, and COPh, can be estimated by using the effect of Me_3N^+ as a model for the polar effect.[20] For the GCH_2SO_2Ph system the resonance to polar ratios determined in this way for G are PhCO (3.7) > NO_2 (1.5), CN (1.4), $PhSO_2$ (1.3). For the GCH_2CN system the ratios are 4.2 for PhCO, 1.6 for CN, and 1.5 for $PhSO_2$. The agreement for the two systems is reasonably good, suggesting that steric inhibition of resonance is not a serious problem. With G = Ph the resonance to polar ratio is 6.6 when EWG is $PhSO_2$, 6.1 when EWG is CN, and 4.6 when EWG is PhCO.[21] The latter value is near the ratio of 4:1 estimated for Ph from the data for the 9,10-dihydroanthracene and xanthene systems where the resonance effect was damped out by steric effects thus allowing an estimate of the polar effect to be made (see above). The results indicate that the resonance to polar ratio for phenyl is much larger than for any of the strong electron-withdrawing groups, only the PhCO group approaching it in this respect. This was not anticipated from other estimates of the relative size of resonance and polar effects for Ph. For example, the $\sigma_{R(A^-)}$ value for Ph, which is a measure of the resonance effect of a *p*-Ph on the acidity in the $ArNH_3^+$ (or ArOH) system, is only 0.04, whereas σ_I for Ph, which measures the polar contribution, is 0.10.[22] [Similarly, Swain and Lupton in their analysis assign a larger polar constant to phenyl ($\mathcal{F}$ = 0.139) than a resonance constant ($\mathcal{R}$ = −0.088).[23]] Part of the difference can be ascribed to the fact that the $\sigma_{R(A^-)}$ value is derived from data for a nitrogen or oxygen acid, rather than a carbon acid. Thus the σ_p^- for Ph derived for the $ArCH_2CN$ system is 0.17,[24] as compared to σ_p^- for Ph of 0.11 derived from phenols.[25] Nevertheless, it would appear that the resonance effect of Ph is severely damped by transmission across a benzene ring, and that the magnitude of its resonance stabilizing effect on carbanions has not been fully appreciated hitherto.

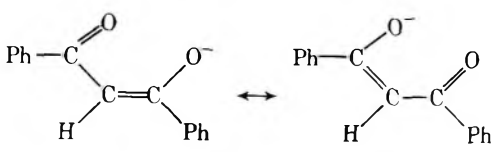
Judging from the GCH_2CN system (see Table II and ref 20) the resonance stabilizing effect of Ph (relative to Me) is 9.1 pK units (12.5 kcal/mol) as compared to 12.2, 13.3, and 18.0 pK units for the $PhSO_2$, CN, and PhCO groups, respectively. In the GCH_2COPh system the acidifying resonance effects of $PhSO_2$, CN, and PhCO have decreased to 6.2, 7.5, and 7.7 pK units, respectively, whereas that of Ph has decreased to only 5.5 pK units. In this system the resonance acidifying effect of Ph is of a magnitude comparable to that of a strong electron-withdrawing group. The diminution of effects in the GCH_2COPh system is in part due to a resonance saturation effect,[13] but this should affect Ph to at least as great a degree as for other substituents. It seems most likely that the unusually severe steric requirements of the GCH_2COPh system (see above) are mainly responsible for the diminution of the effects of $PhSO_2$, CN, and PhCO. For these dipolar substituents there are no doubt substantial repulsive interactions

Table IV

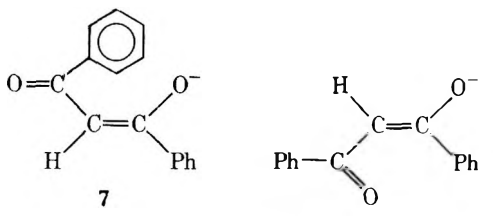
Compd	Mp or bp, °C	Lit. value, °C	Ref
9-Phenyl-9,10-dihydroanthracene	mp 88–89[a]	89	27
9-Phenylxanthene	mp 145[a]	145	2
Phenylnitromethane	bp 99–102 (5 mm)	93–97 (3 mm)	28
α,α-Diphenylacetophenone	mp 136.5–137.5[a]	135–137	29
α,α,α′,α′-Tetraphenylacetone	mp 134–134.5[a]	133–134	30
Diphenylmethyl phenyl sulfone	mp 187–188[a]	187–188	31
Bis(diphenylmethyl) sulfone	mp 192–193[a,c]	185–186	32
Diphenylmethyl phenyl sulfoxide	mp 138–139[b]	137–138	33

[a] Recrystallized from 95% EtOH. [b] Recrystallized from CH_3OH/H_2O. [c] Decomposes on melting.

between the negative charge on the enolate oxygen atom and that on the oxygen atom of the carbonyl group, e.g., as in **6**. (Steric hindrance is severe in conformation **7** and in the *Z* isomer, **8**.) On the other hand, when G = Ph the steric interactions are less severe (see **4**).



6a **6b**



7 **8**

Steric inhibition of resonance in the GCH_2COPh systems causes the resonance to polar ratios, as determined by the use of Me_3N^+ as a model for the polar effect,[20] to drop to 2.1 for PhCO, 2.5 for CH_3CO, 1.1 for CN, 0.91 for $PhSO_2$, and 1.1 for NO_2. The resonance to polar ratio for Ph drops to 4.6, but this is believed to be due primarily to a resonance saturation effect, rather than to steric inhibition of resonance. This view is supported by the parallel effects in GCH_2EWG systems reported in this series for Ph and PhS;[7] steric effects for PhS groups are shown in this paper to be minimal.

Experimental Section

The equilibrium acidity measurements were carried out as previously described.[2,15] With the exception of the trifluoromethyl sulfones and the compounds listed in Table IV, all compounds in Tables II and III are commercially available from the Aldrich or Parish Chemical Co. Samples of methyl, ethyl, and benzyl trifluoromethyl sulfone were kindly provided by J. B. Hendrickson and P. L. Skipper of Brandeis University. The remaining compounds are listed in Table IV along with a reference to their method of preparation. All samples were 99+% pure as judged by TLC or GLC analyses.

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Carbon Acids. 13. Acidifying Effects of Phenylthio Substituents

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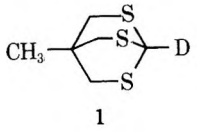
Replacement of a methyl group in $MeCH_2EWG$ parent carbon acids by a phenylthio group leads to an increase in equilibrium acidities in Me_2SO ranging from 4.9 to 11.5 pK units, depending on the nature of EWG (NO_2, F_3CSO_2, PhCO, CH_3CO, $PhSO_2$, CN). The progressively smaller effect observed as the acidity of the parent acid increases is attributed to a resonance saturation effect. The acidifying effects of PhS are comparable in magnitude to those of Ph, and change in the same way with changes in parent acid acidities. In more crowded systems Ph groups are subject to steric inhibition of resonance, but PhS groups are not. Separation of polar and resonance effects of PhS by using Me_3N^+ as a model for the polar effect suggests that strong conjugative interactions exist between PhS and an adjacent carbanion. Comparison of acidities of 2-phenyl-1,3-dithiane and of 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane with those of open-chain analogues failed to reveal any stereoelectronic requirements for these conjugative interactions. Extrapolation indicates that the pK in Me_2SO is 44 for toluene.

There is a voluminous literature indicating that α-PhS (or, to a somewhat lesser degree, α-RS) groups increase the acidity of the adjacent C–H bond, and that this effect is associated with the ability of divalent sulfur to stabilize a negative charge on an adjacent carbon atom.[2] The evidence includes a demonstrated ability of one or more α-PhS (or α-RS) groups to facilitate (1) metalation of C–H, (2) deuterium exchange of C–H, (3) base-initiated β-elimination, (4) tautomerism, (5) Michael addition, and (6) decarboxylation.[2] Most experimentalists have attributed this C–H acidifying or carbanion stabilizing effect to conjugation of the incipient carbanion or the "free" carbanion with the adjacent sulfur atom, the d orbitals on sulfur presumably being involved.[2] From studies of deuterium exchange, or the like, in cyclic molecules containing two or three sulfur atoms several authors have drawn the conclusion that stereoelectronic factors may be important in deciding carbanion stabilities. For example, the fact that the base-initiated deuterium exchange of the bridgehead proton in 4-methyl-2,6,7-trithiabicyclo[2.2.2]-octane (1) is about 10^3 faster than that in an open-chain analogue (2) has been interpreted to mean that the incipient carbanion is stabilized by orbital overlap involving the carbanion and the three sulfur atoms.[3] Strong conjugative interactions involving d orbitals on two or more sulfur atoms and an adjacent carbanion have also been postulated to explain a number of related phenomena, such as the formation of a dilithium derivative of tetrathiadamantane (3).[4]



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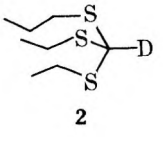

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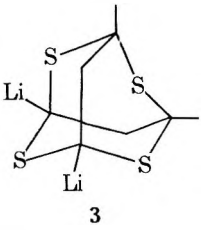


3

There has also been considerable theoretical interest in the bonding characteristics of sulfur in all of its various oxidation states. The d orbitals of divalent sulfur have been described as being far too diffuse for bonding purposes, but theory predicts that attachment of electron-attracting ligands will contract the d orbitals and enhance their bonding properties.[5] In a recent review Coulson concluded that d orbitals are suitable for effecting polarization of p orbitals, but noted that little or no chemical relevance should be attached to the small d-orbital populations arising from this.[6] In considering the bonding in hypervalent molecules, such as SF_6, Musher concluded that "there is little need to introduce d orbitals . . . and that their inclusion is neither crucial nor qualitatively necessary."[7] Similar conclusions concerning the relative unimportance of d orbital participation has been arrived at by Florey and Cusachs for phosphorus and sulfur compounds.[8]

Recent ab initio calculations have indicated that d-orbital conjugation is irrelevant for stabilization of the $HSCH_2^-$ anion, and that the stabilizing effect of sulfur is due to its polarizability.[9] Similar conclusions have been drawn from calculations made on the $HSOCH_2^-$ and $HSO_2CH_2^-$ anions.[10]

The evidence in the literature for stabilization of a carbanion or an incipient carbanion by α-PhS (or α-RS) is compelling, but the magnitude of the effect, its nature, and the reality of the stereoelectronic effects that have been postulated are open to question. In making comparisons many of the earlier studies used α-PhO and α-RO groups as models. It was argued that, since the polar effect of PhO (or RO) is larger than that of PhS (or RS), the greater effects observed with α-PhS (or RS) than with their oxygen analogues must be due to some kind of special stabilizing effect (e.g., d-orbital conjugation). There is also evidence from deuterium exchange studies[11] and from equilibrium acidity measurements,[12] however, to indicate that MeO groups may *destabilize* adjacent carbanions. The question then becomes: how much of the observed difference in the apparent effect on carbanion stability of, say PhS vs. PhO, is caused by a destabilizing effect of oxygen, and how much is caused by a stabilizing effect of sulfur?

The reality of the postulated stereoelectronic effects of sulfur on carbanion stability is open to question because of the difficulty in interpreting some of the data. In some instances ion pair stability, rather than carbanion stability, may be involved. For example, the equatorial preference for the "carbanion" formed by deprotonation of 1,3-dithiane can be accounted for in terms of an equatorially held lithium ion,[13a] as well as by a stereoelectronically favorable p–d overlap,[3] or a "gauche effect".[13b] If carbanion stabilities are to be correctly judged from deuterium exchange studies, it is necessary that the exchange give a true measure of the rate of carbanion formation, which is not always the case.[14] It is also necessary that a good estimate of the size of the Bronsted coefficient be obtained; this too poses problems.[14] Equilibrium acidity measurements for weak acids in dimethyl sulfoxide (Me_2SO) solution provide a quantitative method of determining relative substituent effects. Assuming that the substituents are exerting their effects primarily by stabilizing the anion, as seems likely, in the systems being considered herein, this provides a quantitative measure of anion stabilities free of counterion influences.[15] In a preliminary report we showed that the

Table I. Acidifying Effect in Dimethyl Sulfoxide Solution of the Phenylthio Group in Methane and Ethane Parent Carbon Acids

Registry no.	Parent acid	pK[a]	p$K(\alpha$ − PhS)[a]	ΔpK_H[b]	Registry no.	Parent acid	pK[a]	ΔpK_{Me}[c]
75-05-8	CH_3CN	31.3	20.8	10.7	107-12-0	$MeCH_2CN$	~32.5[d]	~11.5[d]
3112-85-4	CH_3SO_2Ph	29.0	20.3	8.9	599-70-2	$MeCH_2SO_2Ph$	31.0	10.7
67-64-1	CH_3COCH_3	26.5	18.7	8.3	96-22-0	$(MeCH_2)_2CO$	27.1	8.7
98-86-2	CH_3COPh	24.7	17.1	7.8	93-55-0	$MeCH_2COPh$	24.4	7.3
421-82-9	$CH_3SO_2CF_3$	18.8	11.0	8.0	13003-57-1	$MeCH_2SO_2CF_3$	20.4	9.4
75-52-5	CH_3NO_2	17.2	11.8	5.6	79-24-3	$MeCH_2NO_2$	16.7	4.9
1070-92-4	$CH_2(SO_2Et)_2$	14.4	7.1	7.6	32341-85-8	$MeCH(SO_2Et)_2$	16.7	9.6
3406-02-8	$CH_2(SO_2Ph)_2$	12.2	5.6[e]	6.9	33419-26-0	$MeCH(SO_2Ph)_2$	14.3_5	8.7

[a] Runs were made against at least two indicators; standard deviations within runs are generally less than ±0.05 pK unit and those for runs with different indicators are generally less than ±0.1 pK unit. [b] ΔpK_H = pK(HCH_2EWG) − pK($PhSCH_2EWG$); statistically corrected for the number of acidic hydrogen atoms. [c] ΔpK_{Me} = pK($MeCH_2EWG$) − pK($PhSCH_2EWG$). [d] Assuming that the methyl effect on CH_3CN is comparable to that on $PhCH_2CN$ and $CH_2(CN)_2$ as parent acids (ca. 1 pK unit).[16] [e] Measured only against a new indicator, 2,6-di-*tert*-butyl-4-nitrophenol (pK = 7.3). [A previous pK value of 7.6 was obtained potentiometrically by I. M. Kolthoff, M. K. Chantooni, Jr., and S. Bhomik, *J. Am. Chem. Soc.*, **90**, 23 (1968).] Calculation of the pK value for the sulfone neglected the effects of self-ionization in Me_2SO which could lead to a greater uncertainty in the value obtained. Unpublished work from these laboratories and the work of Koltoff et al. cited above would indicate, however, that only a small amount of self-ionization should occur with an acid of this pK at these concentrations (≈10^{-3} M).

acidifying effect of an α-PhS substituent is large in four different carbon acid systems.[12] In the present paper we (a) report the acidifying effects of α-PhS on a variety of other carbon acid systems, (b) compare the effects with those of a phenyl group, (c) determine the size of the polar contribution to this acidifying effect by using the Me_3N^+ substituent as a model, and (d) examine the effect of incorporating the acidifying sulfur atoms into ring systems.

Results and Discussion

Acidifying Effects of the Phenylthio Group. In Table I the acidifying effect of the PhS group is compared to that of a hydrogen atom (ΔpK_H) or a methyl group (ΔpK_{Me}) for a variety of parent carbon acids, mostly of the type HCH_2EWG or $MeCH_2EWG$, where EWG is a strong electron-withdrawing group. Examination of Table I shows that the acidifying effects of PhS, as judged by either reference to a hydrogen atom, i.e., ΔpK_H = pK(HCH_2EWG) − pK($PhSCH_2EWG$) or a methyl group, i.e., ΔpK_{Me} = pK($MeCH_2EWG$) − pK($PhSCH_2EWG$), is large, ranging from 4.9 to 11.5 pK units. The magnitude of the effect varies somewhat depending on whether the methane or ethane carbon acid listed in Table I is used as a model. As was brought out in a previous paper,[12] neither H nor Me is a good model for PhS sterically or electronically, but methyl is no doubt the better model, and will be used in subsequent discussions.

Saturation of Phenylthio Effects. Examination of the ΔpK_{Me} column in Table I shows that, for $PhSCH_2EWG$ carbon acids, the acidifying effect of the PhS group, relative to Me, decreases from 11.5 for the weakest carbon acid, propionitrile, to 4.9 for the strongest carbon acid, nitroethane. The decrease is a progressive one, but not a regular one. A plot of ΔpK_{Me} for the PhS effect vs. pK for $MeCH_2EWG$ gives a smooth curve for the "planar" functions CN, CH_3CO, PhCO, and NO_2 (Figure 1). The $PhSO_2$ point deviated but little from this curve, but the SO_2CF_3 point deviated markedly. The question arose as to whether the F_3CSO_2 point is deviant or whether the points for sulfones in general are deviant, the $PhSO_2$ point happening to fall fortuitously near the curve for the "planar" functions. Inclusion of the points for $MeCH(SO_2Ph)_2$ and $MeCH(SO_2Et)_2$ as parent acids appears to answer this question unambiguously, the latter points falling near the line drawn between the $PhSO_2$ and F_3CSO_2 points, and deviating markedly from the curve. Therefore, the points for the "planar" functions fall on a curve, and the points for the (tetrahedral) sulfone functions fall on a different curve

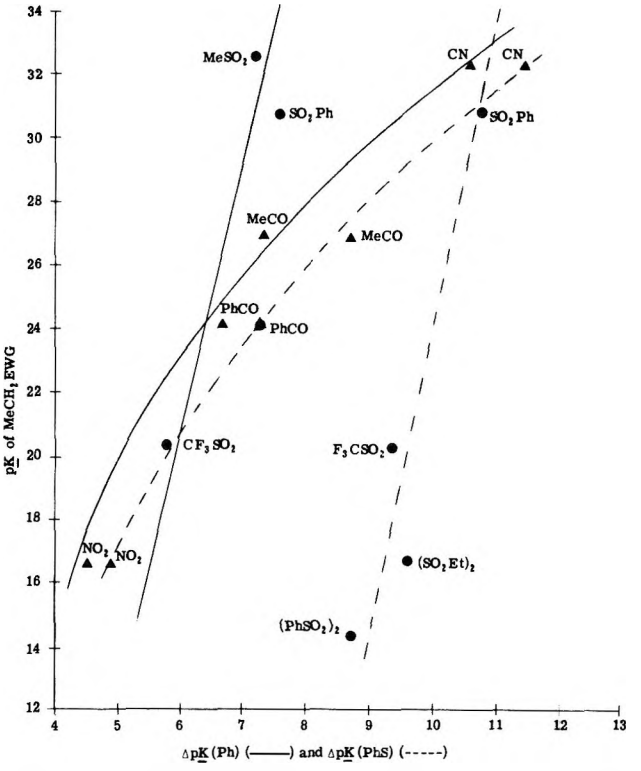


Figure 1. Comparison of phenyl (—) and phenylthio acidifying effects (- - - -) on parent ethane carbon acids, $MeCH_2EWG$, when EWG is a planar function (▲) and a tetrahedral (sulfone) function (●).

(or line). A similar observation has been made for the acidifying effect of a phenyl group on these two types of functions.[17] In fact, plotting ΔpK for the Ph and the PhS acidifying effects vs. the pK of the ethane carbon acids, $MeCH_2EWG$, gives parallel curves for the "planar" functions and roughly parallel lines for the tetrahedral functions (Figure 1). (The resonance to polar ratio for sulfoxide and sulfone functions apparently increases to a lesser degree with increasing acidity than is true for "planar" functions, causing the two types to fall on separate lines.[17])

In the previous paper in this series we assumed that for a series of methane carbon acids, HCH_2EWG, or ethane carbon acids, $MeCH_2EWG$, replacement of H or Me by Ph would cause relatively constant changes in solvation and steric effects.[17] The parallel behavior of Ph and PhS (Figure 1) sup-

Table II. Estimation of the Polar Effect (ΔpK_{calcd}) and Conjugative Effect ($\Delta\Delta pK$) for PhS using Me_3N^+ as a Model for the Polar Effect

Registry no.	G	σ_I[a]	ΔpK_{calcd}[f]	ΔpK_{obsd}[g]	$\Delta\Delta pK$[i]
	A. GCH_2CN Carbon Acids; $\rho_I = 14.5$[12]				
	Me	−0.04[b]	(0.0)	(0.0)	
6340-35-8	Me_3N^+	0.82[c]	(11.9)	11.9	
5219-61-4	PhS	0.30[d]	4.4	11.7	7.3
140-29-4	Ph	0.10	1.5	10.6	9.1
	B. GCH_2SO_2Ph Carbon Acids; $\rho_I = 14.1$[12]				
	Me	−0.04[b]	(0.0	(0.0)	
60595-13-3	Me_3N^+	0.82[c]	(11.6)	11.6	
15296-86-3	PhS	0.30[d]	4.2	10.5	6.3
3112-88-7	Ph	0.10	1.4	7.6	6.2
	C. GCH_2COPh Carbon Acids; $\rho_I = 11.9$[12]				
	Me	−0.04[b]	(0.0)	(0.0)	
16222-10-9	Me_3N^+	0.82[c]	(9.8)	9.8	
60595-14-4	PhS	0.30[d]	3.6	7.3	3.7
35050-01-2	PhSe	0.24[e]	2.9	5.8	2.9
451-40-1	Ph	0.10	1.2	6.7	5.5
	D. 9-G-Fluorene Carbon Acids; $\rho_I = 8.1$[h]				
17114-78-2	Me_3C	−0.07[b]	(0.0)		
6634-60-2	Me_3N^+	0.82[c]	(6.55)	6.55[h]	
	PhS	0.30[d]	2.4	6.9	4.5
	Ph	0.10	0.8	4.4	3.6

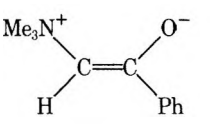
[a] From J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1975, unless otherwise noted. [b] Taken as 0.0. [c] An average value; see ref 12 for a discussion. [d] M. Charton, *J. Org. Chem.*, **29**, 1222 (1964). [e] Calculated from $\sigma^*CH_2SePh = 0.45$, obtained from the data of L. D. Pettit, A. Royston, C. Sherrington, and R. J. Whewell, *J. Chem. Soc. B*, 588 (1968). [f] From $\Delta pK = \sigma_I\rho_I$. [g] Relative to the p$K$ of $MeCH_2CN$ (32.5; series A), or $MeCH_2SO_2Ph$ (31.0; series B) or $MeCH_2COPh$ (24.4, series C), or 9-methylfluorene (22.3, series D). [h] Relative to 9-*tert*-butylfluorene (pK = 24.35). [i] $\Delta\Delta pK = \Delta pK_{obsd} - \Delta pK_{calcd}$.

ports this assumption. In particular, since, as will be brought out shortly, we have found that the Ph effect is highly sensitive to steric inhibition of resonance, whereas PhS is not, the parallel behavior of the two groups indicates that, for this series of carbon acids, steric inhibition of resonance is unimportant.

The Trimethylammonio Group as a Polar Model. In an earlier paper in this series the trimethylammonio group, Me_3N^+, was used as a model to deduce the size of the polar effect of the phenylthio group, as well as a number of other groups, in GCH_2EWG carbon acid systems. The difference in acidity between $MeCH_2EWG$ and $Me_3N^+CH_2EWG$ for EWG = CN, SO_2Ph, and COPh was used to calculate a ρ_I from the Taft equation, $\Delta pK = \sigma_I\rho_I$, and the σ_I for PhS was used to calculate the size of the polar effect.[12] The results of this analysis for the phenylthio group are shown in Table II, together with a similar analysis for the phenyl group.

Examination of Table II shows that in the GCH_2CN system the acidifying effect of PhS observed is 7.3 pK units greater than that calculated for a polar effect. Somewhat smaller, but still large, differences are observed for the GCH_2SO_2Ph and GCH_2COPh systems ($\Delta\Delta pK$ = 6.3 and 3.7, respectively). These differences are presumably due to an effect other than an electrostatic effect. A conjugative effect of some type between the negatively charged carbon atom and the adjacent sulfur atom is indicated. The smaller effect observed for the GCH_2COPh system is probably the result of a steric effect of some kind. (In the previous paper we have presented evidence to show that this system is highly sensitive to steric effects.[17]) For example, if the structures of the enolate ions are **4** and **5**, respectively, the calculated polar effect would be enhanced by the proximity of the charged groups in **4**.

The magnitude of the acidifying effect of the PhS group is brought out further by a direct comparison of pK's:



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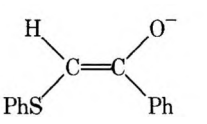

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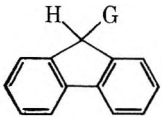


6

$PhSCH_2CN$, 20.8 vs. $Me_3N^+CH_2CN$, 20.6, and $PhSCH_2SO_2Ph$, 20.3 vs. $Me_3N^+CH_2SO_2Ph$, 19.4. In the fluorene system (**6**) the PhS group produces a 2.4 pK unit *greater* acidifying effect than does Me_3N^+ (pK = 15.4 for **6** with G = PhS vs. 17.8 for G = Me_3N^+). Here, however, a steric effect is probably decreasing the effect of Me_3N^+, since 9-*tert*-butylfluorene is 2.2 pK units weaker than 9-methylfluorene. Nevertheless, here, as well as in the other instances, it is clear that the PhS group is producing a far greater acidifying effect than is expected from its polar effect, as judged by the Taft equation.

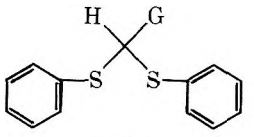
If $\Delta\Delta pK$ in Table II is taken as the size of the resonance effect, we see that for the first three carbon acid systems the resonance effect is appreciably larger for Ph than for PhS. The order is reversed for the fluorene system, but here the effect of Ph is subject to steric inhibition of resonance, whereas the PhS effect is not (see the next section). Nevertheless, even in this instance the resonance to polar ratio is much larger for Ph (4.9) than for PhS (1.9). For PhS the resonance to polar ratio ($\Delta\Delta pK/\Delta pK_{calcd}$ from Table II) is 1.6 for EWG = CN, 1.5 for EWG = $PhSO_2$, and 1.0 for EWG = COPh. These ratios are smaller than observed for Ph or CH_3CO, but are about the same size as those observed for NO_2, CN, or $PhSO_2$.[17] The resonance to polar ratio for the PhS group derived from the data in Table II is larger than 1.0, whereas the ratio of $\sigma_{R(A)}$- to σ_I is less than 1.0. This is typical of electron-withdrawing groups known to enter into conjugative interactions with anions, such as Ph, NO_2, CN, and $PhSO_2$.[17] The evidence is

consistent, then, with a conjugative interaction between PhS and the carbanion.[21]

A polarizability effect for PhS could also be involved to some extent since polarizability effects are known to fall off rapidly with distance. If the PhS effect is caused just by a polarizability effect, however, the larger and more polarizable selenium atom would be expected to have a still *larger* effect, but it does not. In the GCH_2COPh system $PhSeCH_2COPh$ has a pK of 18.6 as compared to 17.3 for $PhSCH_2COPh$. In terms of the analysis used in Table II, the PhSe group has a larger effect than expected from its σ_I constant, but the increase ($\Delta\Delta pK$) is smaller for PhSe than for PhS (2.9 vs. 3.7). The acidifying order PhS > PhSe is that expected for a conjugative effect, the orbitals of the larger selenium atom being less effective than sulfur in overlapping with the p orbital of the much smaller carbon atom in the anion.

Steric Demands of Phenylthio and Phenyl Groups. In the previous paper it was shown that, when a phenyl group is substituted for a hydrogen atom in a carbon acid already containing two substituents, as for $PhCH_2EWG \rightarrow Ph_2CHEWG$ or $PhCH_2Ph \rightarrow Ph_2CHPh$, the acidifying effect of the second phenyl group is greatly decreased.[17] This is in part due to a resonance saturation effect, but the major cause is steric inhibition of resonance. One would not anticipate that the acidifying effect of the phenylthio group would be subject to comparable steric restrictions since there is no reason to expect that the π system of its phenyl ring need adopt any particular orientation with respect to the p orbital of the carbanion. In agreement with this expectation it was found that, contrary to the behavior of the phenyl group, introduction of a PhS group into a disubstituted carbon acid caused a large acidifying effect. For example, whereas a 9-phenyl substituent increases the acidity of xanthene by only 2.4 pK units, a 9-phenylthio substituent causes a 7.5 pK unit increase in acidity. Table III provides a comparison of phenyl and phenylthio effects in a series of di- and trisubstituted carbon acids.

Examination of Table III shows that the acidifying effect of phenyl is only 2 pK units for substitution into $PhCH_2Ph$, increases to 4.4 pK units for substitution into $PhCH_2SPh$, and to 8.1 pK units for substitution into $PhSCH_2SPh$. On the other hand, the acidifying effect of the PhS group is large (5.9–8.3 pK units) for substitution into any of these three substrates. Evidently there is appreciable steric inhibition of resonance of the phenyl groups in the Ph_2CSPh^- anion, but less so than in the Ph_3C^- anion. The acidifying effect of the PhS group does not appear to be subject to any appreciable steric inhibition of resonance. This is brought out further by the comparisons of pK's given under formulas **7–10**.



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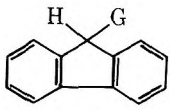

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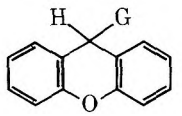

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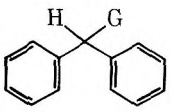


10

G	pK	ΔpK	pK	ΔpK	pK	ΔpK	pK	ΔpK
H	30.8		22.6		30.0		32.3	
Ph	23.0	8.1	17.9	5.0	27.9	2.4	30.6	2.0
PhS	22.8	8.3	15.4	7.5	22.8	7.5	26.7	5.9

In the series **7, 8, 9, 10**, judging from the progressive decrease in the size of the acidifying effect of phenyl from ΔpK 8.1 in **7** to 2.0 in **10**, it is apparent that there is a progressive increase in steric hindrance as we proceed from **7** to **10**. The fact that the acidifying effect of PhS decreases but little in this series indicates that its steric demands are minimal. Even in the Ph_2CHG system (**10**), where the apparent PhS effect has decreased from 8.3 (for **7**) to 5.9 pK units, it is probably not a requirement for a particular orientation of the PhS group, relative to the p orbital of the carbanion, that causes the reduced effect, but rather a decrease in the overlap of the π systems of the phenyl groups with the p orbital of the carbanion resulting from increased crowding.

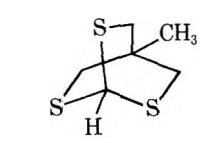
Table III. Comparison of the Acidifying Effects of Ph and PhS in $PhCH_2Ph$, $PhCH_2SPh$, and $PhSCH_2SPh$ Substrates

Acid	pK[a]	ΔpK(Ph)[b]	ΔpK(PhS)[b]
$PhCH_2Ph$	32.3		
$PhCH_2SPh$	30.8		
$PhSCH_2SPh$	30.8		
Ph_2CHPh	30.6	2.0[c]	
Ph_2CHSPh	26.7	4.4[d]	5.9[c]
$PhCH(SPh)_2$	23.0	8.1[e]	8.1[d]
$PhSCH(SPh)_2$	22.8		8.3[e]

[a] Equilibrium acidity in Me_2SO;[15] not statistically corrected. [b] Statistically corrected for the number of acidic hydrogen atoms. [c] Relative to $PhCH_2Ph$. [d] Relative to $PhCH_2SPh$. [e] Relative to $PhSCH_2SPh$.

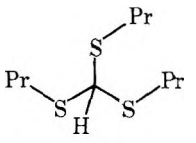
In the absence of steric effects we have suggested that, as a first approximation, the size of a substituent effect will be regulated by the negative charge density at the carbon atom in the anion to which the substituent is attached.[17,18] In view of the near constancy in the size of the PhS effect for carbon acid systems **7–10**, it would appear, then, that the negative charge density differs but little at the acidic site in the anions derived from these acids. For **7, 9,** and **10** this is not surprising since the acidities of the parent acids differ by only a few pK units. The fluorene system (**8**) differs sharply from the others, however. Note, for example, that the PhS effect is as large for **8** as for **9**, despite the 7.4 pK unit greater acidity of **8**. This suggests that a greater fraction of the negative charge in the fluorenyl anion remains at the 9 position, for aromaticity reasons, than is true for the xanthenyl anion. Delocalization of the negative charge in the $(PhS)_2CH^-$ anion to the benzene rings can occur only through the sulfur atoms. It is remarkable, then, that the charge density at the acidic site in the $(PhS)_2CH^-$ anion is no larger than at the 9 position in the fluorenyl or xanthenyl anions as judged by the PhS effect. It would appear that the sulfur atoms have been able to cause an effective decrease in the charge density in the anion, probably by some kind of conjugative interaction. This view is consistent with the observation that the acidifying effect is *smaller* for $CH_2(SPh)_2$ than for CH_3CN (ΔpK = 8.3 vs. 10.6). In the CH_2CN^- anion it seems clear that the charge density at carbon must be markedly decreased by delocalization to nitrogen;[22] it seems likely that the charge density in the $(PhS)_2CH^-$ ion is also decreased by delocalization.

The equilibrium acidities of **11**, the protio derivative of **1**, its acyclic analogue (**12**), 2-phenyl-1,3-dithiane (**13**), and an acyclic analogue (**14**) were examined in order to learn something of the stereoelectronic requirements, if any, of divalent sulfur. It has been suggested that sulfur atoms constrained in rings may provide more effective p–d overlap to carbanions in these ring systems.[3,4] For example, the approximately 10^3 faster rate for **11** than for an acyclic analogue, such as **12**,[3] could mean that the equilibrium acidity of **11** would be as much as 6 pK units greater than that for **12** (assuming a "normal" Bronsted coefficient of 0.5). The results of our equilibrium measurements show that **11** is more acidic than



11

pK = 30.5



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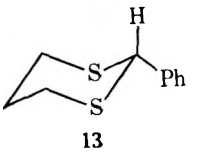
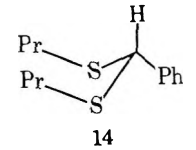
pK = 31.3



13

pK = 30.7



14

pK = 29.2

12, but the difference is small (0.8 pK unit). Examination of scalar molecular models shows that the p orbital of the carbanion derived from **12** may be completely shielded from the solvent by the alkyl groups. On the other hand, the pyramidal carbanion derived from **11** is open to solvation from the "front" side, but screened from solvation from the "back" side. It seems likely that these differences in solvation of the anions are the cause of the difference in acidities, and that no appreciable stereoelectronic effect is present.

No special stereoelectronic effect arising from incorporation of the sulfur atoms into a ring is apparent from the pK data for **13** and **14**. The ring compound is less acidic by 1.5 pK units, but again it seems likely that this relatively small difference is caused by a solvent effect of some kind.

Extrapolation to Obtain the pK of Toluene. Knowing the approximate magnitude of the acidifying effect of a PhS substituent and the approximate degree to which this acidifying effect is attenuated by delocalization of the charge in the system to which it is attached, we can make a rough estimate of the acidity of toluene, a hydrocarbon much too weakly acidic to be measured in Me_2SO solution. Since we can expect the negative charge in the $PhCH_2^-$ ion to be strongly delocalized into the benzene ring, the resonance saturation effect caused by Ph in this anion will be large, and the effect of substituting a group like PhS for an α-hydrogen atom into this anion will be strongly attenuated relative to that for substitution into an anion of comparable stability in which the charge is less delocalized. The Ph group in the $PhCH_2^-$ ion can be likened in this respect to the PhCO group in the $PhCOCH_2^-$ ion. As pointed out earlier, both groups have large resonance to polar ratios. Judging from the tangent of the PhS curve at the PhCO point (Figure 1), the attenuation in the size of the PhS acidifying effect caused by PhCO in the $PhCOCHSPh^-$ ion is about 3.5 pK units per 10 pK unit change in parent acid acidities. We can expect a proportional effect for Ph in $PhCH_2^-$, but since the parent acid ($PhCH_3$) in this instance has a pK roughly 20 pK units higher than that of $PhCOCH_3$, the total attenuation of the PhS effect due to resonance saturation will be about 7 pK units for substitution of PhS into toluene. The total PhS acidifying effect will then be this value plus the size of the acidifying effect cf PhS on $PhCOCH_3$ ($\approx$7.5 pK units). This places the pK of toluene about 14.5 pK units above that of $PhSCH_2Ph$ or $\approx$45. Similar extrapolations using the 14.4 pK unit acidifying effect of the CN group on $PhCOCH_3$,[12] or the 13.2 pK unit acidifying effect of the $PhSO_2$ group on $PhCOCH_3$,[12] give slightly lower values.

$$PhSCH_2Ph \xrightarrow{+7.5 + 2(3.5)} HCH_2Ph$$
$$pK\ 30.8 \qquad (pK \cong 45)$$

$$PhCH_2CN \xrightarrow{+14.4 + 2(3.5)} HCH_2Ph$$
$$pK\ 21.9 \qquad (pK \cong 43)$$

$$PhCH_2SO_2Ph \xrightarrow{+13.2 + 2(3.5)} HCH_2Ph$$
$$pK\ 23.4 \qquad (pK \cong 44)$$

These extrapolations are rough since they depend heavily on the value of 3.5 per 10 pK units chosen for the attenuation of the PhS effect, and since they assume that the same attenuation will apply for the CN and $PhSO_2$ groups. The average value of 44 $\pm$ 1 obtained agrees reasonably well, however, with the value of 41 arrived at for toluene by Streitwieser by extrapolation of a Bronsted plot.[22] (Our pK's in Me_2SO agree well with Streitwieser's ion pair pK's in cyclohexylamine for hydrocarbons forming highly delocalized anions.[15])

Conclusions Regarding Conjugation of Carbanions and Adjacent Sulfur Functions. In this paper we have shown that the acidifying effect of substituting PhS for Me in a variety of carbon acids, $MeCH_2EWG$, is comparable to that of a phenyl substituent in type and magnitude. The acidifying effect of PhS in a number of carbon acid systems has been shown to be almost as large as that of the much polar substituent, Me_3N^+. Arguments have been presented to support the conclusion that a large portion of this PhS effect is due to the ability of the sulfur atom to stabilize the charge on an adjacent negatively charged carbon atom by a conjugative effect, possibly utilizing d orbitals. According to our present estimates, substitution of PhS for a hydrogen atom in methane causes an increase in acidity in Me_2SO of a minimum of 17 pK units, equivalent at 25 °C to 23 kcal/mol stabilization of the carbanion. Increasing the oxidation state of sulfur, as in CH_3SO and CH_3SO_2, causes additional increases in acidity amounting to about 13 and 17 pK units, respectively. Evidence has been presented recently to show that sulfone functions exert strong conjugative interactions with adjacent carbanions.[24] We believe that conjugation is strong between, not only sulfone functions and adjacent carbanions, but also, to a lesser degree, between carbanions and adjacent sulfoxide and sulfide functions.

Two theoretical papers have appeared within the past few months each stressing the importance of stereoelectronic effects in stabilizing an adjacent carbanion and each denying the stabilizing effect of sulfur d orbitals.[46,47] Both papers cite comparisons of kinetic acidities, e.g., **11** with **12**,[3] as experimental support for stereoelectronic effects. In contrast, we find the differences in equilibrium acidities in Me_2SO solution between **11** and **12** to be small.

Experimental Section

The equilibrium acidity measurements were carried out as previously described.[15] Samples of methyl and ethyl trifluoromethyl sulfone were kindly provided by J. B. Hendrickson and P. L. Skipper of Brandeis University, while 2-phenyl-1,3-dithiane was provided by N. H. Andersen of the University of Washington. The syntheses and properties of 9-*tert*-butyl-, 9-phenylthio-, and 9-phenylfluorene and 9-phenylxanthene have been previously reported.[15] Other compounds listed in the text or tables are commercially available from the Aldrich or Parish Chemical Co. The remaining compounds are listed in Table IV, or below, with a reference to their method of preparation. All samples were 99+% pure as judged by the TLC or GLC analyses.

Phenylthiomethyl Trifluoromethyl Sulfone. Trifluoromethanesulfonyl chloride (5 g, 30 mmol, Aldrich Chemical Co.) was reduced with potassium iodide to potassium trifluoromethanesulfinate by the literature procedure.[40] To 4 g (23 mmol) of this salt in 30 ml of acetonitrile freshly distilled from P_2O_5 was added 3.9 ml (~23 mmol) of chloromethyl phenyl sulfide[41] and 0.35 g (2.1 mmol) of potassium iodide as catalyst. This mixture was refluxed overnight, then stirred for a further day at 25 °C, whereupon the resulting dark brown solution containing a yellowish-white precipitate was poured into water containing an excess of sodium thiosulfate. Extraction with dichloromethane, washing with water and brine, and drying ($MgSO_4$) gave 3.9 g of a brown oil after concentration in vacuo. Short-path vacuum distillation yielded 1.1 ml of a yellow oil as the major fraction, bp 100–115 °C (0.35–0.5 mm). This was purified by filtration through grade I alumina with dichloromethane as eluent, followed by repeated recrystallization from pentane at −78 °C to give white needles which melted below room temperature to a colorless oil. This oil was identified as pure phenylthiomethyl trifluoromethyl sulfone: NMR δ 4.39 (s, 2, $-CH_2-$) and 7.15–7.68 (m, 5, ArH); IR 1370 (s), 1120 (s) (sulfone),

Table IV. Physical Properties of Acids Listed in the Text

Compd	Mp or bp, °C	Lit. value, °C
Phenylthiomethyl phenyl sulfone	61–62	62[25]
Bis(ethylsulfonyl)methane	102.5–103.5	103–104[26]
1,1-Bis(ethylsulfonyl)ethane	74–75	75–76[26]
1,1-Bis(phenylsulfonyl)ethane	102–103	101–102[27]
Benzhydryl phenyl sulfide	78	78[28]
α,α′-Bis(*n*-propylthio)toluene (14)	114 (0.5 mm)	Not reported[29]
Tris(*n*-propylthio)methane (12)	83 (0.05 mm)	158–60 (12 mm)[30]
Tris(phenylthio)methane	42–42.5	39[31]
α,α′-Bis(phenylthio)toluene	50.5–51.5	48.5–51[32]
9-(Phenylthio)xanthene	77	78–79[33]
4-Methyl-2,6,7-trithiabicyclo-[2.2.2]octane (11)	130	130.5–131[34]
Bis(ethylsulfonyl)phenylthio-methane	83–83.5	86[35]
Bis(phenylsulfonyl)phenyl-thiomethane	178.5–179.5	179–180[36]
(9-Fluorenyl)trimethylammo-nium bromide	189–190 dec	189–190 dec[37]
(Cyanomethyltrimethylam-monium chloride	180 dec	186–189[38]
2,6-Di-*tert*-butyl-4-nitrophenol	156–157	156[39]

and 1210 cm^{-1} (br, s) cm^{-1} (CF_3). Anal. Calcd for $C_8H_7F_3O_2S_2$: C, 37.49; H, 2.75. Found: C, 37.43; H, 2.78.

Phenylthionitromethane. Following the general procedure of Mukaiyama,[42] ethyl nitroacetate (3.9 g, 38 mmol) and 4-(phenylthio)morpholine[43] (6.5 g, 38 mmol) were placed in 50 ml of dichloromethane. After the solution had stood at room temperature for 3 h, removal of solvent under reduced pressure gave a tan salt which was taken up in a solution of 8.6 g of potassium hydroxide in 75 ml of water and 50 ml of ethanol and heated for 0.75 h on a steam bath. The ethanol was removed under reduced pressure, and the aqueous mixture was acidified to pH 7 with 10% HCl. Then 10 g (140 mmol) of hydroxylamine hydrochloride in 20 ml of water was added to the aqueous solution at 0 °C over 10 min. Extraction with three 100-ml portions of ether afforded, upon workup, 5 ml of yellow oil, 92% pure by GC and NMR. Column chromatography on silica with CCl_4 as eluent gave a pale yellow material 99+% pure by GLC: n^{23}D 1.5785; NMR ($CDCl_3$) δ 5.38 (s, 2, $-CH_2-$) and 7.1–7.5 (m, 5, ArH); ir 1550 and 1350 cm^{-1} ($-NO_2$). Anal. Calcd for $C_7H_7NO_2S$; C, 49.69; H, 4.17; S, 18.95. Found: C, 49.64; H, 4.23; S, 18.79.

(Phenylsulfonylmethyl)trimethylammonium Chloride. Crude (phenylthiomethyl)trimethylammonium chloride (0.7 g, 3.2 mmol), prepared from chloromethyl phenyl sulfide[41] and anhydrous trimethylamine in ethanol, was dissolved in 50 ml of HOAc. To this solution was added 2 ml of 30% aqueous H_2O_2 and the mixture was heated upon a steam bath for 12 h. Aqueous workup followed by extraction with ethyl acetate and evaporation of the aqueous layer resulted in an oil which showed spectral characteristics of a sulfoxide. This material was then dissolved in 20 ml of HOAc and oxidized further by 5 ml of 30% H_2O_2 by the above procedure for another 18 h with workup as above. The oily residue was triturated with $CHCl_3$, resulting in crystals which were filtered and washed with $CHCl_3$. Recrystallization from CH_3CN–EtOH gave crystals: mp 181.5–183.5 °C; NMR (Me_2SO-d_6 and D_2O) δ 3.30 (s, 9, CH_3), 5.28 (s, 2, CH_2), and 7.6–8.2 (m, 5, ArH); IR (KBr) 1325 (s) and 1160 cm^{-1} (s) (sulfone).

Anal. Calcd for $C_{19}H_{16}ClNO_2S$: C, 48.09; H, 6.46. Found: C, 47.85; H, 6.50.

α-Phenylselenoacetophenone. A sample of α-acetoxystyrene (1.62 g, 0.01 mol, prepared by the method of Noyce and Pollack[44]) added dropwise, with stirring to a solution of benzeneselenyl chloride (1.9 g, 0.01 mol, prepared by the method of Behaghel and Seibert[45]) in CH_2Cl_2 (10 ml). The red color of the selenyl chloride disappeared during the addition. The mixture was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated, leaving the crude phenylselenoacetophenone as a thick yellow oil. Twelve recrystallizations from ether/pentane at −78 °C produced the pure material as white platelets: mp 40–41 °C; NMR ($CDCl_3$) δ 4.15 (s, 2, CH_2), 7.1–8.0 (m, 10, aryl H); ir (mull) 1667 cm^{-1} (C=O).

(Phenacyl)trimethylammonium Chloride. Phenacyl chloride (3.1 g, 20 mmol) and 2 ml of trimethylamine were dissolved in 20 ml of EtOH and refluxed for 3.5 h. After cooling to room temperature, 100 ml of ether was added, followed by filtration of the resulting white crystals. Recrystallization from acetonitrile gave white crystals: mp 203–205 °C; NMR (Me_2SO-d_6) δ 3.35 (s, 9, CH_3), 5.55 (s, 2, CH_2), 7.4–8.1 (m, 5, ArH).

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Registry No.—**7** (G = H), 3561-67-9; **7** (G = Ph), 7695-69-4; **7** (G = PhS), 4832-52-4; **8** (G = H), 86-73-7; **8** (G = Ph), 789-24-2; **8** (G = PhS), 28114-92-3; **9** (G = H), 92-83-1; **9** (G = Ph), 3246-80-8; **9** (G = PhS), 35595-00-7; **10** (G = H), 101-81-5; **10** (G = Ph), 519-73-3; **10** (G = PhS), 21122-20-3; **11**, 39137-60-5; **13**, 5425-44-5; **14**, 60595-12-2; phenylthiomethyl trifluoromethyl sulfone, 60595-15-5; trifluoromethanesulfonyl chloride, 421-83-0; chloromethyl phenyl sulfide, 7205-91-6; phenylthionitromethane, 60595-16-6; ethyl nitroacetate, 626-35-7; 4-(phenylthio)morpholine, 4837-31-4; (phenylthiomethyl)trimethylammonium chloride, 25803-80-9; α-acetoxystyrene, 2206-94-2; benzeneselenyl chloride, 5707-04-0; phenacyl chloride, 532-27-4; trimethylamine, 75-50-3; dimethyl sulfoxide, 67-68-5.

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Rates of Thiol–Disulfide Interchange Reactions between Mono- and Dithiols and Ellman's Reagent[1]

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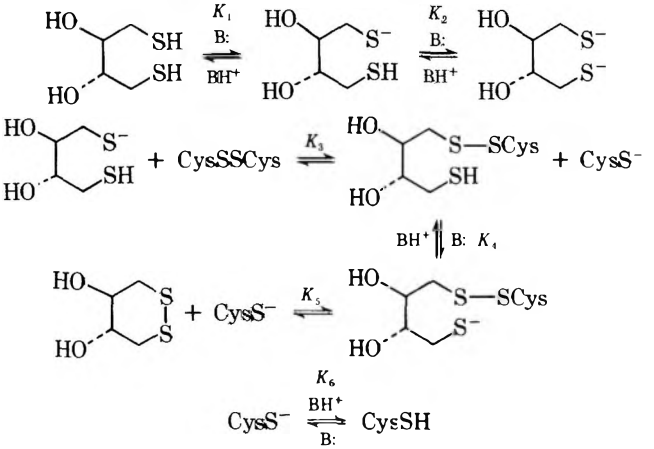
The rate constants for thiol–disulfide interchange between 21 mono- and dithiols and Ellman's reagent correlate with the pK_a's of the thiol groups with a Bronsted coefficient of $\beta = 0.36$. The maximum rates of reduction are observed for thiols having pK_a values close to the pH of the solution in which the reactions were carried out. In the dilute solutions examined (10^{-4}–10^{-6} M in each reagent), the rate of the second, intramolecular interchange step in reactions of dithiols was faster than that of the first, intermolecular interchange, regardless of the size of the cyclic disulfide formed. A convenient synthesis of a mixture of diastereomers of 1,4-dimercapto-2,3-butanediol (i.e., of a mixture of dithiothreitol, DTT, and dithioerythritol, DTE) has been developed from 1,2:,4-diepoxybutane and thiolacetic acid.

Oxidation of cysteine sulfhydryl groups during isolation, storage, and use of proteins is often an important contributor to their deactivation.[2] Although the rate of oxidation can be decreased by limiting access of oxygen to the enzyme, it is usually impractical to exclude oxygen completely, particularly in practical synthetic and analytical applications. The most effective and widely used reagents for protecting the cysteine moieties of enzymes against oxidation by adventitious oxygen, and for activating partially oxidized and deactivated enzymes by reduction, are thiols, particularly dithiothreitol (DTT, Cleland's reagent)[3] and β-mercaptoethanol. Each has its advantages and disadvantages: DTT reduces protein disulfide groups rapidly and completely and is convenient to handle, but is exorbitantly expensive; β-mercaptoethanol is readily available and inexpensive, but reacts less rapidly and completely.

As part of a project designed to develop techniques to permit the use of enzymes as catalysts in large-scale organic synthesis, we required an agent that would reduce disulfide moieties more rapidly and completely than β-mercaptoethanol but which would be less expensive than DTT. The design of an appropriate reagent is not straightforward for several reasons. First, the mechanism of reduction (illustrated in Scheme I for DTT) involves multiple acid–base and sulfhydryl–disulfide interchange equilibria, and the dependence of the overall rate and equilibrium position on the structure of the reducing agent (and possibly of the protein) is difficult to predict. An important part of the difference in reactivity between DTT and β-mercaptoethanol can, however, plausibly be attributed to the rate of release of the second equivalent of $CysS^-$ (or CysSH) from initially formed mixed disulfides: since β-mercaptoethanol is commonly used in enzymology at concentrations of ca. 10 mM, the rate of the intermolecular reaction involved in its release of CysSH from $CysS-CH_2CH_2OH$ should be approximately 10^{-3}–10^{-4} the rate of the corresponding intramolecular release from $CysS-CH_2CHOHCHOHCH_2SH$. Second, a useful reducing reagent,

Scheme I. Mechanism of Reduction of a Cystine Moiety CysS–SCys by DTT



in addition to high reactivity and ready availability, should also have good water solubility, tolerable odor, and low toxicity. These requirements seriously limit the range of possible thiols.

Here we describe an examination of the rates of reaction of a number of mono- and dithiols with 5,5′-dithiobis(2-nitrobenzoic acid) (Ellman's reagent, EllS-SEll).[4] This study represents the first phase of an effort to understand the kinetics and equilibria of biochemically relevant thiol–disulfide interchange reactions in sufficient detail to be able to rationalize the exceptionally useful properties of DTT in terms of its structure, and to design alternative, effective reducing agents. Ellman's reagent was chosen as the disulfide for initial examination for several reasons. First, since the S–S bond is weak, its reduction by most thiols should be complete: it should thus be possible to examine the influence of the structure of a reducing thiol on its rate of reaction with the disulfide bond of Ellman's reagent without complications by

a competing reverse reaction. Second, the reduction of Ellman's reagent is easily followed spectrophotometrically. Third, Ellman's reagent is a reagent widely used for the determination of sulfhydryl groups, and information concerning the rates of its reduction by thiols should be useful in these other applications.

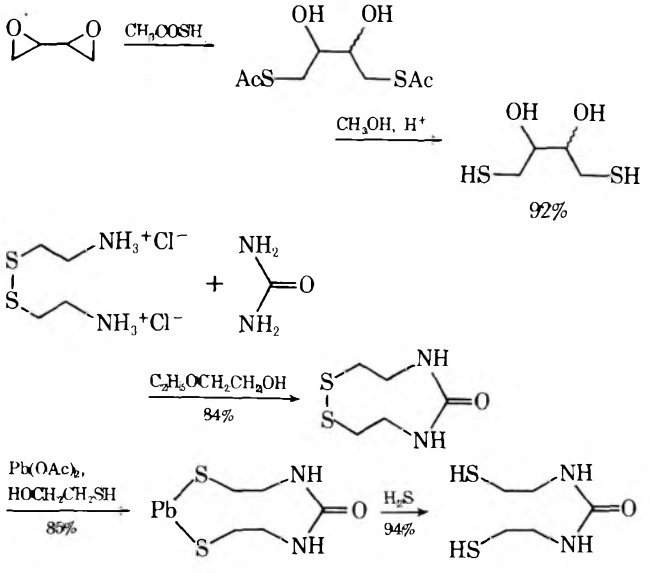
Although data obtained from these studies cannot be applied directly to the design of reagents for the reduction of protein disulfide moieties, they should provide answers to two fundamental questions that underlie this problem: Do the rates of reduction of a particular disulfide moiety by thiol reducing agents and the pK_a's of the SH groups of these reducing agents obey a Bronsted relation? What is the optimum pK_a for the thiol group of a reducing agent intended to be used at a particular solution pH?

Results

Synthesis of Sulfhydryl Reducing Agents. All of the characteristics of DTT as a reagent for reducing disulfide moieties are satisfactory except for its expense. A solution to the problem of providing an effective, inexpensive reducing agent could come either from a reduction in the cost of DTT, or by developing an alternative, easily prepared, material having comparable properties.

DTT is prepared from 1,4-dibromo-2-butene by a four-step stereospecific synthesis.[5] Since DTT and DTE have similar activity, and since their enantiomeric and diastereomeric purity is almost certainly irrelevant in most applications, this synthesis is unnecessarily complicated. It proved possible to prepare mixtures of diastereomeric 1,4-dimercapto-2,3-butanediols in excellent yield by reaction of 1,2:3,4-diepoxybutane with thiolacetic acid[6] followed by acid-catalyzed deacylation (transesterification) in methanol (Scheme II). The

Scheme II. Synthesis of 1,4-Dimercapto-2,3-butanediol and *N,N'*-Bis(2-mercaptoethyl)urea

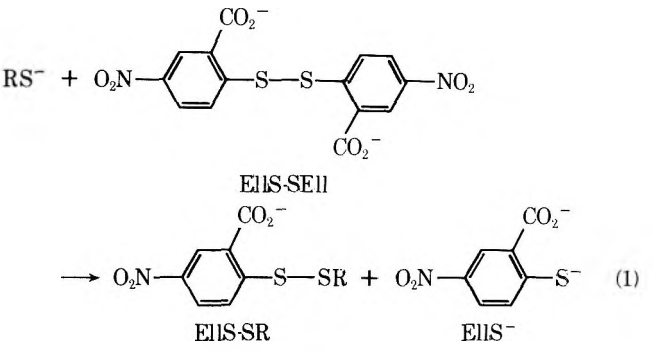


direction of the acid-catalyzed epoxide opening is presumably controlled by the inductive effect of the adjacent oxygens.[7] A preparation of the same dithiol from hydrogen sulfide and diepoxybutane is reported in the patent literature.[8] Diepoxybutane is prepared by oxidation of butadiene,[9] and its generation and utilization in situ should decrease the problems of toxicity and storage stability associated with the pure compound.

Preparation of thiols and disulfides from halides and tosylates is often cumbersome: commonly used procedures have been reviewed[10] and most appear impractical as the basis for large-scale synthesis. We have examined several routes based on condensation reactions: one sequence, leading from cystamine hydrochloride and urea to *N,N'*-bis(2-mercaptoethyl)urea, is outlined in Scheme II. In this and related efforts, it proved most convenient for small-scale work initially to prepare and purify disulfides and subsequently to reduce these to the desired dithiols, rather than toprepare the dithiols directly.

Measurements of Rates of Reduction of Ellman's Reagent by Thiols. Rates were obtained at 30.0 °C and pH 7.0 (0.05 M phosphate buffer) in oxygen-free solutions containing Ellman's reagent and (di)thiol by following the absorbance with time at 412 nm, the λ_{max} for the anion of 2-nitro-5-thiobenzoic acid (Ellman's anion); Ellman's reagent itself does not absorb significantly at this wavelength. At pH 7.0, the generation of Ellman's anion by reaction of Ellman's reagent with hydroxide ion[11] was insignificant compared with its production by reaction with thiol. Control experiments established that low concentrations of added copper(II) salts had no influence on the measured rates, provided that oxygen was excluded. As expected, copper(II) was an active catalyst for oxidation by air.[12] Irradiation with uv light also had no influence on rates. The thiol–disulfide interchange appears to be influenced by buffer concentration and composition: all reactions were therefore carried out using a standard buffer and concentration (0.05 M phosphate).

The kinetic schemes used as the basis for analyzing the reduction of Ellman's reagent by mono- and dithiols are defined in the following equations.



For monothiols

$$RSH \overset{K_a}{\rightleftharpoons} RS^- + H^+ \quad (2)$$

$$RS^- + EllS\text{-}SEll \xrightarrow{k_1} RS\text{-}SEll + EllS^- \quad (3)$$

$$RS^- + RS\text{-}SEll \xrightarrow{k_2} RS\text{-}SR + EllS^- \quad (4)$$

$$d(EllS^-)/dt = k_1^{obsd}[(RS^-) + (RSH)](EllS\text{-}SEll) + k_2^{obsd}[(RS^-) + (RSH)](EllS\text{-}SR) \quad (5)$$

Here k_1^{obsd} and k_2^{obsd} are observed rate constants based on an experimental rate equation (5) containing terms in the total concentration of sulfhydryl species $[(RS^-) + (RSH)]$, and k_1 and k_2 are rate constants for reactions involving the thiolate anions (reactions 3 and 4). This problem requires analysis of competitive, consecutive, second-order reactions.[13] Preliminary analysis showed that $k_1 > 10k_2$. It was possible to take advantage of this difference in rate constants to separate the terms in k_1^{obsd} and k_2^{obsd} in eq 5 by fixing the relative concentrations of reducing agent and Ellman's reagent so that the contribution of either reaction 3 or reaction 4 to the production of $EllS^-$ was negligible. Thus, to obtain k_1^{obsd}, the initial concentration of thiol reagent was set at any value less than one-half that of Ellman's reagent (eq 6).

$$2[(RS^-) + (RSH)]_0 \leq (EllS\text{-}SEll)_0 \quad (6)$$

Table I. Rate Constants (k, M^{-1} s^{-1}) for Reduction of Ellman's Reagent by Mono- and Dithiols[a]

Registry no.		Thiol	pK_a	k_1^{obsd}	k_2^{obsd}	k_1	k_2	Solubility[b]
98-91-9	1	C_6H_5COSH	2.48[c]	1.0×10^2	39.4	1.0×10^2	39.4	$\leq 10^{-2}$
507-09-5	2	CH_3COSH	3.5[d]	2.0×10^2	82.3	2.0×10^2	82.3	>1
3814-18-4	3	m-$NO_2C_6H_4SH$[e]	5.24[f]	1.4×10^4	g	1.5×10^4	g	$\leq 10^{-2}$
1074-36-8	4	p-$HO_2CC_6H_4SH$[h]	5.80[i]	1.3×10^4	g	1.3×10^4	g	$\leq 10^{-2}$
106-53-6	5	p-BrC_6H_4SH	6.02[f]	3.1×10^4	g	3.5×10^4	g	$\leq 10^{-2}$
15570-12-4	6	m-$CH_3OC_6H_4SH$	6.39[f]	4.1×10^4	g	5.1×10^4	g	$\leq 10^{-2}$
137-07-5	7	o-$NH_2C_6H_4SH$	6.59[j]	3.3×10^4	g	4.6×10^4	g	$\leq 10^{-2}$
108-98-5	8	C_6H_5SH	6.62[f]	1.6×10^4	g	2.6×10^4	g	$\leq 10^{-3}$
123-81-9	9	$(HSCH_2CO_2CH_2)_2$	7.70 (8.97)	8.8×10^3	k	5.2×10^4	k	$\leq 10^{-2}$
760-30-5	10	$H_2NNHCOCH_2SH$	7.75	7.8×10^3	g	5.1×10^4	g	$\sim 10^{-1}$
59-52-9	11	$HOCH_2CHSHCH_2SH$	8.59 (10.5)	2.7×10^3	k	1.1×10^5	k	≥ 1
584-04-3	12	$HSCH_2CHOHCH_2SH$	9.04 (10.3)	2.6×10^3	k	2.8×10^5	k	≥ 1
3570-55-6	13	$(HSCH_2CH_2)_2S$	9.09 (10.1)	2.5×10^3	k	3.1×10^5	k	$\leq 10^{-3}$
6892-68-8	14	DTT	9.21 (10.1)	2.5×10^3	k	2.9×10^5	k	≥ 1
3483-12-3	15	DTT/DTE[l]	9.2 (10.1)	2.3×10^3	k	2.7×10^5	k	≥ 1
60633-86-5	16	$(HSCH_2CH_2NH)_2CO$	9.26 (10.0)	2.1×10^3	k	2.5×10^5	k	$\leq 5 \times 10^{-3}$
2150-02-9	17	$(HSCH_2CH_2)_2O$	9.21 (9.91)	5.4×10^2	k	8.7×10^4	k	$\leq 10^{-2}$
60-24-2	18	$HOCH_2CH_2SH$[m]	9.5[n]	6.2×10^2	28	2.0×10^5	8.7×10^3	≥ 1
96-27-5	19	$HOCH_2CHOHCH_2SH$	9.5[d]	1.0×10^3	20	3.2×10^5	6.4×10^3	≥ 1
68-11-1	20	$HSCH_2CO_2H$	9.8[n]	3.0×10^2	2.7	1.8×10^5	2.1×10^3	≥ 1
1191-08-8	21	$HS(CH_2)_4SH$	9.98 (10.7)	9.4×10^2	k	9.0×10^5	k	$\leq 10^{-3}$

[a] All rates were obtained in 0.05 M phosphate buffer, pH 7.0, 30.0 °C containing 10^{-6} M EDTA under an argon atmosphere. Rate constants have the units M^{-1} s^{-1}. [b] Approximate limiting solubility (M) in this buffer system. [c] J. Hipkin and D. P. N. Satchell, *Tetrahedron*, **21**, 835 (1965). [d] J. P. Danehy and K. N. Parameswaran, *J. Chem. Eng. Data*, **13**, 386 (1968). [e] Prepared by reduction [C. R. Stahl and S. Siggia, *Anal. Chem.*, **29**, 154 (1957)] of the corresponding disulfide (W. A. Sheppard, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 843). [f] P. DeMaria, A. Fini, and F. M. Hall, *J. Chem. Soc., Perkin Trans. 2*, 1969 (1973). [g] Not determined. [h] L. Nelander, *Acta Chem. Scand.*, **18**, 973 (1964). [i] R. J. Irving, L. Nelander, and I. Wadso, *ibid.*, **18**, 769 (1964). [j] M. R. Crampton, *J. Chem. Soc. B*, 2112 (1971). [k] The rate of reaction 15 (text) was greater than that of reaction 13: k_2^{obsd} and k_2 could not be determined. [l] A mixture of diastereomers prepared from diepoxybutane. [m] In 0.05 M HEPES buffer (pH 6.9), $k_1^{obsd} = 2.2 \times 10^2$ M^{-1} s^{-1}; in 0.05 M TEA buffer (pH 6.9), $k_1^{obsd} = 3.0 \times 10^2$ M^{-1} s^{-1}. [n] Reference 15.

$$d(EllS^-)/dt \simeq k_1^{obsd}[(RS^-) + (RSH)](EllS\text{-}SEll) \quad (7)$$

Under these conditions, reaction 4 does not contribute significantly to the production of $EllS^-$, and the rate expression 5 can be approximated by the simplified expression of eq 7. Similarly, by setting the initial concentration of Ellman's reagent to be less than that of thiol (typically a factor of 10: eq 8), production of $EllS^-$ occurs in two kinetically distinct phases: an initial, fast phase corresponding to reaction 3 in which the Ellman's reagent is converted essentially quantitatively to EllS-SR, followed by a slower phase (reaction 4), which can be described by the approximate rate expression 9.

$$[(RS^-) + (RSH)]_0 \geq 10(EllS\text{-}SEll)_0 \quad (8)$$

$$d(EllS^-)/dt \simeq k_2^{obsd}[(RS^-) + (RSH)]_0(EllS\text{-}SR) \quad (9)$$

Equation 7 can be integrated by standard procedures to yield eq 10.[13] Equation 9 is treated similarly.

$$\frac{1}{[(RS^-) + (RSH)]_0 - (EllS\text{-}SEll)_0} \times \ln \frac{(EllS\text{-}SEll)_0}{[(RS^-) + (RSH)]_0} \left[\frac{[(RS^-) + (RSH)]_0 - (EllS^-)}{(EllS\text{-}SEll)_0 - (EllS^-)} \right] = k_1^{obsd}t \quad (10)$$

Since the reactivity of the thiolate anion, RS^-, is so much greater than that of the thiol, RSH, any contribution to the generation of $EllS^-$ from the latter can be neglected. The observed rate constants k^{obsd} and the rate constants for reaction of thiolate anion k (eq 3, 4) can then be related by eq 11a: here pK_a is defined by the acid dissociation of the thiol (eq 2), and pH is that of the solution (in these experiments, pH 7.00).

$$k_1 = k_1^{obsd}[1 + 10^{pK_a - pH}] \quad (11a)$$

$$k_2 = k_2^{obsd}[1 + 10^{pK_a - pH}] \quad (11b)$$

For dithiols

$$HSRSH \overset{K_a}{\rightleftharpoons} HSRS^- + H^+ \quad (12)$$

$$HSRS^- \overset{K'_a}{\rightleftharpoons} {}^-SRS^- + H^+ \quad (12a)$$

$$HSRS^- + EllS\text{-}SEll \xrightarrow{k_1} HSRS\text{-}SEll + EllS^- \quad (13)$$

$${}^-SRS^- + EllS\text{-}SEll \xrightarrow{k'_1} {}^-SRS\text{-}SEll + EllS^- \quad (13a)$$

$$HSRS\text{-}SEll \overset{K''_a}{\rightleftharpoons} {}^-SRS\text{-}SEll \quad (14)$$

$${}^-SRS\text{-}SEll \xrightarrow{k_2} SRS + EllS^- \quad (15)$$

$$HSRS\text{-}SEll + HSRS^- \xrightarrow{k_3} HSRS\text{-}SRSH + EllS^- \quad (16)$$

We simplify this set of equations by noting that these reactions occur in dilute solutions (10^{-4}–10^{-6} M), and then assuming that, under these circumstances, the intermolecular thiol–disulfide interchange involving the mixed disulfide (reaction 16) does not compete with the intramolecular reaction (reaction 15). The correctness of this assumption clearly depends on the relative magnitudes of k_2 and k_3. If the ring formed in reaction 15 were sufficiently strained, this reaction might, in principle, be much slower than reaction 16 even in dilute solution. On the basis of limited precedent, however, it seems unlikely that ring strain in five-, six-, and seven-membered cyclic disulfides would be sufficient to decrease k_2

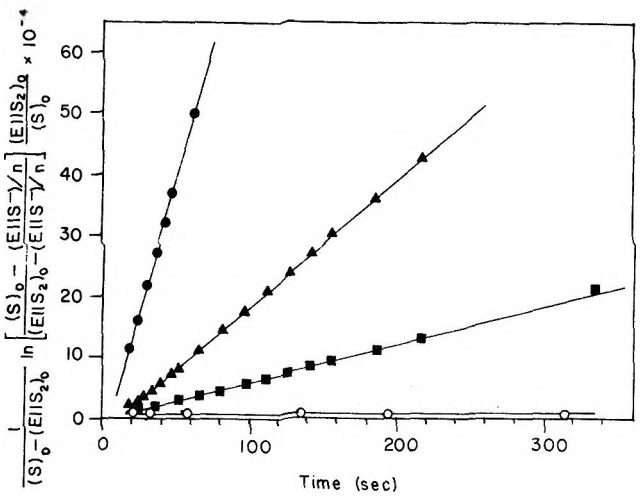


Figure 1. Rate constant plots for the reaction of several mono- and dithiols with Ellman's reagent in pH 7.0 phosphate buffer (0.05 M) at 30.0 ± 0.5 °C under argon. The terms in the expression on the axis are defined as follows: for the monothiols, $S_0 = [(RS^-) + (RSH)]$, $n = 1$; for the dithiols, $S_0 = [(^-SRS^-) + (HSRS^-) + (HSRSH)]$, $n = 2$ (cf. eq 10 and 18 of the text). Reducing agents: ●, glycol dimercaptoacetate; ■, bis(2-mercaptoethyl) ether; ▲; *N,N'*-bis(2-mercaptoethyl)urea; ○, thioglycolic acid.

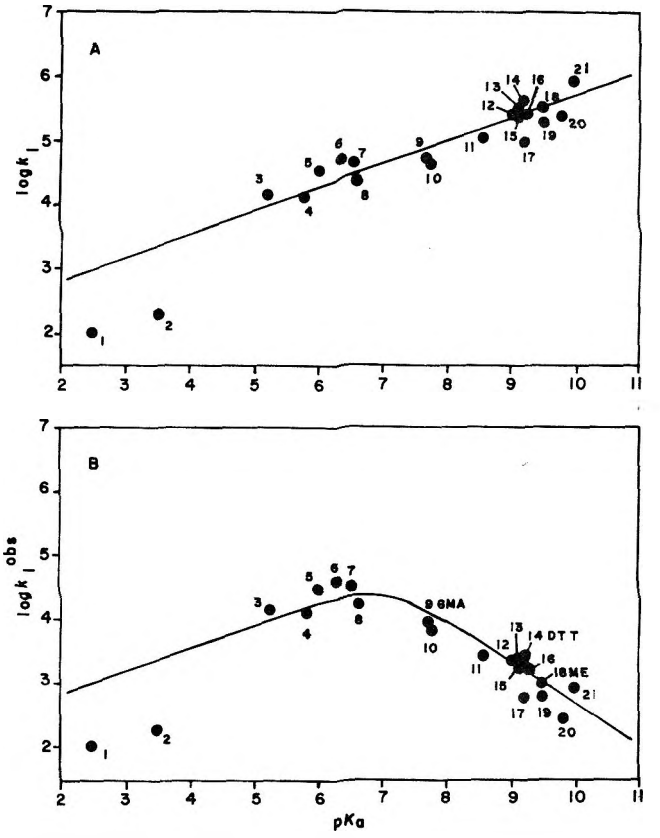


Figure 2. Plots of (A) log k_1 and (B) log k_1^{obsd} vs. pK_a for reduction of Ellman's reagent in pH 7.0 phosphate buffer (0.05 M) at 30.0 ± 0.5 °C under argon with the mono- and dithiols listed in Table I. The equations used to generate the solid lines are (A) $\log k_1 = 2.1 + 0.36\ pK_a$; (B) $\log k_1^{obsd} = 2.1 + 0.36\ pK_a - \log(10^{pK_a - 7.0} + 1)$. The numbers refer to Table I. DTT is dithiothreitol; ME is β-mercaptoethanol; GMA is glycol dimercaptoacetate. The parameters for the Bronsted line (log $G = 2.1$, $\beta = 0.36$) were estimated neglecting the thiol acids (points 1 and 2).

to the point where the rates of reactions 15 and 16 would be comparable.[14] There is no way of estimating ring strain in large rings containing many heteroatoms [e.g., that from *N,N'*-bis(2-mercaptoethyl)urea], but this strain is almost certainly less than that in saturated carbocycles of the same size.

With these approximations, analysis of the experimental data obtained from solutions of Ellman's reagent and dithiols becomes closely analogous to that for monothiols. A rate equation of the form 17 was followed. In this equation, $(S_{total}) = [(^-SRS^-) + (^-SRSH) + (HSRSH)]$.

$$d(EllS^-)/dt \cong 2k_1^{obsd}(S_{total})(EllS\text{-}SEll) \qquad (17)$$

Straightforward consideration of material balance permits the variable concentrations in the equation to be expressed in terms of ($EllS^-$) and the resulting expression integrated as eq 18.

$$\frac{1}{(S_{total})_0 - (EllS\text{-}SEll)_0} \times \ln \frac{(EllS\text{-}SEll)_0}{(S_{total})_0} \left[\frac{(S_{total})_0 - \tfrac{1}{2}(EllS^-)}{(EllS\text{-}SEll)_0 - \tfrac{1}{2}(EllS^-)} \right] = k_1^{obsd} t \qquad (18)$$

The factor of 2 in eq 17 reflects the assumption that reaction 13 is rate limiting, and the production of a second equivalent of $EllS^-$ by reaction 15 follows rapidly, once the intermediate mixed disulfide HSRS-SEll is formed. Experimental support for this assumption derives from the observation in reductions using dithiols that there was no suggestion of the two-stage production of $EllS^-$ characteristic of the monothiols, even when the initial concentration of dithiol was much greater than that of Ellman's reagent: the experimental data were compatible with eq 18.

Without examining the change in k_1^{obsd} with pH there is no method of separating this term into the individual rate constants characteristic of the species lumped under the term S_{total}: viz., $^-SRS^-$, ^-SRSH, and HSRSH. To assign a rate constant, we assume, as previously, that the reactivity of the neutral thiol HSRSH is so low compared to that of the thiolates that it can be neglected, and, further, that $^-SRS^-$ and ^-SRSH are equally reactive. The former assumption is undoubtedly good. The latter is to some extent in error: $^-SRS^-$ will be more reactive than ^-SRSH. The dianion will, however, be present in lower concentrations that the monoanion, and their reactivity difference is probably not large. The rate constant k_1 in reaction 13 can then be approximated by an expression analogous to eq 11. Estimates of k_1 in this manner will be too high since they will include a contribution from the (faster) reaction of the dithiolate species $^-SRS^-$: this inaccuracy may contribute to the scatter in the Bronsted plot derived from these data (vide infra). Since, however, the concentration of $^-SRS^-$ is less than that of ^-SRSH, no statistical correction of these rate constants is required.

Table I summarizes the rate constants derived from kinetic examination of the reduction of Ellman's reagent by various thiols. Three useful facts emerge immediately from analysis of these rate constants. First, the values of k_1 (with the exception of those for thiolacetic and thiobenzoic acid) approximately obey a Bronsted relation, with $\beta = 0.36$ (Figure 2). This value is compatible with values of β found for reactions of thiols with other types of substrates: *N-p*-2-benzimidazolylphenylmaleimide, $\beta = 0.42$;[15] *p*-nitrophenyl acetate, $\beta = 0.38$;[16] ethylene oxide, $\beta = 0.30$;[17] and benzene oxide, $\beta = 0.22$.[18] Second, for the five compounds of Table I for which both k_1 and k_2 were determined, $k_2 \lesssim 0.1k_1$. This conclusion helps to justify the experimental conditions chosen to reduce eq 5 to eq 7 and 9, and to generate eq 17. Third, assuming that the rate of attack of thiol reagent on Ellman's reagent does follow a Bronsted relationship with $\beta = 0.36$, it is possible to derive a relation between thiol pK_a and solution pH that permits a prediction of the pK_a value that will lead to a max-

imum value of k_1^{obsd} at a particular solution pH. By the definition of a Bronsted relation, one can relate k_1^{obsd} to k_1 using eq 19 and 20.

$$k_1 = G10^{\beta pK_a} \quad (19)$$

$$k_1^{obsd} = k_1 \frac{(RS^-)}{(RS^-) + (RSH)} = \frac{G10^{\beta pK_a}}{1 + 10^{pK_a - pH}} \quad (20)$$

Differentiating eq 20 with respect to pK_a, setting $(\partial k_1^{obsd}/\partial pK_a)$ equal to zero, and solving, one obtains eq 21 as the condition for which k_1^{obsd} is a maximum.

$$\frac{1-\beta}{\beta} = 10^{pH-pK_a} \quad (21)$$

Thus, for $\beta = 0.36$, k_1^{obsd} will maximize when $pK_a = pH - 0.25$. Figure 2 plots the values of log k_1^{obsd} and log k_1 from Table I against the thiol pK_a values. This figure also includes a plot of a theoretical curve for log k_1^{obsd} vs. pK_a.

Discussion

The rate constants k_1 characterizing the attack of a number of organic thiolate ions on the disulfide linkage of Ellman's reagent in aqueous solution follow a Bronsted relation: the nucleophilic reactivities of the thiolate ions are directly proportional to their basicity. Since the fraction of a particular thiol present in solution in the reactive thiolate form depends upon the thiol pK_a and the solution pH, k_1 is not, however, the most useful parameter in characterizing the reactivity of a thiol toward Ellman's reagent: the observed rate constants, k_1^{obsd}, provide more direct measures of reactivity. The prediction that k_1^{obsd} for thiols obeying a Bronsted relation with $\beta = 0.36$ should have its maximum value when $pK_a = pH - 0.25$ is supported by experimental data at pH 7 (Figure 2). This figure also indicates that neither of the commonly used reducing agents DTT nor β-mercaptoethanol is the fastest thiol reagent to attack Ellman's reagent in solutions at pH 7: the values of k_1^{obsd} for the various thiophenols listed in Table I are approximately ten times larger than those for DTT and β-mercaptoethanol.

The kinetic behavior of all of the dithiols tested indicates that the initial, intermolecular attack on Ellman's reagent is rate limiting, and that the subsequent, intramolecular step is fast. Four- and five-membered rings (and possibly large rings) containing disulfide linkages are strained. In the dilute solutions studied, however, this strain is evidently not sufficient to cancel the concentration advantage conferred by the intramolecularity of the second reaction.

These results define the influence of thiol structure on the *rate* of its reaction with Ellman's reagent, and suggest two structural features which should be included in new reagents for reduction of cystine disulfide groups. An effective reagent should be a dithiol itself easily capable of forming an intramolecular disulfide, and at least one thiol should have a pK_a close to the pH of the solution in which it is to be used. The properties of DTT are compatible with both of these criteria, although the thiol pK_a values are too high for optimum rates at pH 7.

These data do not in themselves provide an adequate basis for the design of effective reagents for reduction of protein cystine units for two reasons. First, although reduction of Ellman's reagents with the thiols examined here (with the exceptions of the two acidic thio acids) goes to completion, reduction of typical cystine moieties is much less favorable thermodynamically, and the influence of the structure of the dithiol reagent on the equilibrium constant for reduction becomes an important factor. Second, although reduction of Ellman's reagent is a kinetically simple reaction, there is no assurance that electronic factors other than those reflected in a Bronsted plot, or steric or solvation effects, are unimportant in determining the kinetics of reduction of protein cystine groups. In fact, preliminary results in these laboratories indicate no clear correlation between the rates of reduction of Ellman's reagent by thiols and the effectiveness of these substances as reducing agents for proteins.

Experimental Section

General Methods. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. pH was determined using a Radiometer Model 28 pH meter. Infrared spectra were taken using a Perkin-Elmer Model 567 grating spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer. Uv spectra were measured using a Gilford Model 240 spectrometer equipped with a sample chamber thermostated at 30.0 ± 0.5 °C. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionization potential of 20 eV. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J. Distilled water was passed through an ion exchange column and redistilled using a Corning AG-1B still.

Materials. Thin layer chromatography used J. T. Baker silica gel, grade 1 B. Argon (Airco welding grade) was used without further purification. Unless otherwise stated, pure grade solvents were used without further purification. 1,2:3,4-Diepoxybutane was obtained from ROC/RIC, 2,2′-dithiobis(ethylamine) dihydrochloride from Sigma Chemical Co., and dithiodiglycolic acid (96%), thioglycolic acid (98%), methyl thioglycolate (98%), thiolacetic acid (97%), and 2-mercaptoethanol (98%) were obtained from Aldrich Chemical Co. Glycol dimercaptoacetate was a gift of Evans Chemetics, Darien, Conn.

Thiols were either recrystallized or distilled under vacuum. Ellman's reagent (Aldrich, 99%) was used without further purification. All other chemicals used were AR grade.

1,4-Dimercapto-2,3-butanediol (a Mixture of Dithiothreitol and Dithioerythritol). To 48 g (0.63 mol) of thiolacetic acid at 0 °C under argon was added dropwise, with stirring, 25.8 g (0.30 mol) of 1,2:3,4-diepoxybutane followed by 2 ml of methanol. *Caution. Butadiene diepoxide, like many similar dialkylating agents, is mutagenic. It should be used in a good hood, and care taken to avoid contact with liquid or vapor.* The mixture was allowed to stir at room temperature. Within 48 h a crystalline mass of the epimeric 1,4-dimercaptoacetyl-2,3-butanediols had developed. A sample washed free of residual oils with ether–pentane (1:1) showed mp 64–68 °C; ir (CH_2Cl_2) 3400, 2920, 2890, 1720, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.8–3.4 (m, 2), 3.3–2.9 (m, 6), 2.40 (s, 6). This crude material, after treatment at reflux under argon with 150 ml of degassed methanol and a catalytic amount of HCl (2 ml of ~1 N HCl in ether) for 6 h followed by sequential distillation of methyl acetate and methanol, gave 42.8 g (92%) of a diastereomeric mixture of 1,4-dimercapto-2,3-butanediols (bp 120–125 °C at 0.1–0.3 mm) which crystallized on standing in the cold: mp 12–15 °C; ir (film) 3450, 2920, 2550 cm^{-1}; NMR ($CDCl_3$) δ 3.9–3.5 (*m*, 2), 3.3 (*s*, 2), 2.9–2.5 (*m*, 4), 1.66 (t, 2, J = 8 Hz). The distilled product is contaminated with 2–5% of 1,3-dimercapto-2,4-butanediols and related materials. The diastereomeric composition of this material was not examined.

2,9-Diaza-5,6-dithiacyclononanone. In a 2-l. round-bottomed single-necked flask were combined 1.5 l. of distilled 2-ethoxyethanol, urea (9.01 g, 0.15 mol), and cystamine hydrochloride (33.7 g, 0.15 mol). The mixture was flushed with argon for 0.5 h, and refluxed under argon for 14 h. The mixture was cooled to room temperature under argon and filtered, and most of the solvent removed under reduced pressure. The product was precipitated on cooling, isolated, and washed with ether. The remaining 2-ethoxyethanol was removed under reduced pressure, leaving a product which was triturated with methanol to remove the brown gum coating it. A yield of 22.3 g (84%) of 1,9-diaza-5,6-dithiacyclononanone was obtained. The product, after recrystallization from methanol, showed mp 207–208 °C; ir (*Nujol*) 3340, 1625, and 1590 cm^{-1}; NMR (CF_3CO_2H) δ 2.2–2.7 (m, 4), 3.0–3.5 (*m*, 4).

Anal. Calcd for $C_5H_{10}N_2OS_2$: C, 33.69; H, 5.65; N, 15.71; S, 35.97. Found: C, 33.90; H, 5.73; N, 15.57; S, 36.17.

Reaction of Lead(II) Acetate Trihydrate with 2-Mercaptoethanol and 2,9-Diaza-5,6-dithiacyclononanone. Lead(II) acetate (7.2 g, 0.019 mol) and 2,9-diaza-5,6-dithiacyclononanone (3.38 g, 0.019 mol) were added to 350 ml of doubly distilled water and the mixture flushed with argon. 2-Mercaptoethanol (2.66 ml, 0.038 mol) was added by syringe, and the mixture stirred at room temperature for 12 h and refluxed under argon for 7 h. The flask was cooled to 0 °C, and the product filtered and washed with chloroform, to give 6.2 g (85%) of lead(II) 2,2′-dithiodiethylurea as a yellow-orange powder: mp 220 °C

dec; ir (Nujol) 3320, 1620, 1270, 1220, and 625 cm^{-1}; NMR (CF_3CO_2H) δ 2.8 (t, 4, J = 6 Hz) and 3.6 (t, 4, J = 6 Hz).

***N,N'*-Bis(2-mercaptoethyl)urea.** A suspension of lead(II) 2,2'-dithiodiethylurea (3.95 g, 10.25 mmol) in 300 ml of $CHCl_3$ was flushed with argon, and H_2S was bubbled through the suspension for 5 min, during which time the reaction mixture became black. The suspension was flushed with argon for 0.5 h to remove excess H_2S from the solution and filtered under argon through a Celite pad. The solvent was removed under reduced pressure and the pressure restored to 760 mm using nitrogen. The product, a white solid obtained in 94% yield (1.73 g), showed mp 118–119.5 °C; ir (Nujol) 3325, 3140, 1620, 1595, 1275, 1240, 1205, and 665 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, 2, J = 8 Hz, SH), 2.45–2.9 (m, 4, $HSCH_2$), 3.4 (q, 4, J = 6 Hz, $NHCH_2$), and 5.05 (br, 2, NH); mass spectrum (20 eV) m/e M^+ 180.

Anal. Calcd for $C_5H_{12}N_2OS_2$: C, 33.31; H, 6.71; N, 15.54; S, 35.57. Found: C, 33.54; H, 6.48; N, 15.29; S, 35.47.

Thioglycolic Acid Hydrazide. Distilled thioglycolic acid methyl ester (20 ml, 23.06 g, 0.2173 mol) was transferred by syringe into a 500-ml round-bottomed flask which had been flame dried under argon and charged with 250 ml of dry, argon-saturated methanol. To this mixture was added 3.2 ml (0.095 mol) of 95% hydrazine (anhydrous). The reaction mixture was refluxed under argon for 24 h and cooled to room temperature, and the solvent removed under reduced pressure. The resulting solid product was filtered in a glove bag under argon, washed with dry, deaerated ethyl acetate, and dried at 0.01 mm and room temperature for several days. The hygroscopic product, obtained in essentially quantitative yield, had mp 50–52 °C (lit.[19] mp 50–52 °C); ir (Nujol) 3170, 3030, 2920, 2850, 1590, 1490, and 1150 cm^{-1}.

Anal. Calcd for $C_2H_6N_2OS$: C, 22.63; H, 5.70; N, 26.39; S, 30.21. Found, C, 22.73; H, 5.87; N, 25.85; S, 30.60.

Determinations of the extinction coefficient for Ellman's anion, EllS$^-$ were carried out under argon using solutions originally ca. 10^{-4} M in Ellman's reagent and ca. 10^{-3} M in 2-mercaptoethanol: we assumed that the tenfold excess of reducing agent would convert the Ellman's reagent to Ellman's anion quantitatively. Measurements were made carefully at the extinction maximum for the anion: λ_{max} 412 nm. At this frequency absorption due to Ellman's reagent is negligible.[4a,20] Neither 2-mercaptoethanol nor 2,2'-dihydroxydiethyl disulfide absorb at this wavelength. These values of the extinction coefficient were determined (ϵ, pH, buffer, buffer concentration M): 15 000, 9.0, TEA, 0.2; 14 800, 8.0, TEA, 0.2; 14 700, 7.0, TEA, 0.2; 14 600, 5.8, TEA, 0.2; 13 700, 7.0, phosphte, 0.05. This last value is in satisfactory agreement with previous determinations: 13 600, 7.0, phosphate, 0.25;[11c] 13 600, 6.5, phosphate, 0.133.[21] Throughout the work described in this paper, we have used ϵ 13 700. Ellman's reagent (pK_a = 4.75)[11a] is essentially completely ionized in the buffer systems used.

Quantitative Determination of the Rate of Decomposition of Ellman's Reagent. The stoichiometry of the decomposition of Ellman's reagent in base has been determined to be that shown in eq 22.[11c]

$$2EllS\text{-}SEll + 4OH^- \rightarrow 3EllS^- + EllSO_2^- + 2H_2O \qquad (22)$$

This decomposition was followed by measuring the increase in absorbance with time at 412 nm, due to $EllS^-$, in degassed solutions at 30 °C (0.2 M TEA buffers). Reactions were followed over 30 h. Initial slopes [$d(EllS^-)/dt$, M h^{-1}] for solutions initially 9.6×10^{-5} M were 1.38×10^{-6}, pH 9.0; 6.03×10^{-7}, pH 8.0; 1.42×10^{-7}, pH 7.0; 8.88×10^{-8}, pH 5.8. These correspond to decomposition of approximately these percentages of the original Ellman's reagent in 1 h: 1.0%, pH 9.0; 0.4%, pH 8.0; 0.1%, pH 7.0; 0.06%, pH 5.8. These estimates are of the same order of magnitude as reported previously.[11b]

Kinetics of Reduction of Ellman's Reagent by Thiols. One representative kinetic run will be described; others followed similar procedures. Dithiothreitol (DTT, 0.0773 g, 0.501 mmol) was transferred to a 100-ml volumetric flask which had been rinsed with pH 7.0 phosphate buffer solution and flushed with argon. The DTT solution was made up to volume, the volumetric flask stoppered, and the flask flushed with argon for 5 min and mixed by shaking. The stopper was removed and 1.0 ml of the solution was transferred to a 100-ml volumetric flask using an Eppendorf pipet. The solution was made up to volume in a similar manner to give a 0.501×10^{-4} M solution. Five milliliters of this latter solution was transferred to a 50-ml volumetric flask and made up to volume to give a 0.501×10^{-5} M solution. This solution was equilibrated in the 30 °C constant temperature bath connected to the cell compartment of the uv spectrophotometer. The same techniques were used to prepare solutions of Ellman's reagent with concentrations 1.0×10^{-3}, 0.5045×10^{-4}, and 0.5045×10^{-5} M. All solutions were kept under a positive pressure of argon.

Four 1-cm uv cells, fitted with serum stoppers, were flushed with argon. Two milliliters of the 10^{-4} M Ellman's reagent solution was transferred to a cell using a micrometer syringe. The cell was restoppered, equilibrated to 30 °C, and placed in the cell compartment. The spectrometer was zeroed. Two milliliters of the 10^{-4} M DTT solution was drawn into the micrometer syringe, the needle was pushed through the serum stopper of the cell, the recorder was turned on, and the reagent was added as quickly as possible. The reaction was followed by observing the change in absorbance of Ellman's anion at 412 nm; the reaction temperature was recorded before and after the experiment by placing a small EXAX thermometer (14–36 °C) inside the cell compartment. Control experiments included runs in solutions containing DTT but no Ellman's reagent and vice versa, to check for baseline drift. A run containing a ten-fold higher concentration of Ellman's reagent oxidized all of the DTT, and served to check that the starting concentration of DTT calculated from the weight was the same as that found spectrophotometrically. An experiment involving a ten-fold increased concentration of DTT served the same purpose for the Ellman's reagent.

Representative kinetic data are shown in Figure 1. Analysis of these data followed the procedure outlined in the text, and was accomplished by a computer program written for that purpose.[22]

Uv Light Has No Influence on the Thiol–Disulfide Interchange Reaction. Two cells containing Ellman's reagent were prepared at the same time. The cells were equilibrated in the 30 °C bath and placed in the cell compartment. Thioglycolic acid was added to the first cell, and a stopwatch was turned on; as the acid was added to the second cell the stopwatch time was noted and the recorder turned on. Since the solutions were dilute, the reaction was sufficiently slow that inaccuracies caused by this clumsy method of starting the reaction were minor. One of the uv cells was kept almost continuously in the uv light path and the other was placed in the beam only infrequently to take the absorbance readings. Because thioglycolic acid reacts more slowly with Ellman's reagent than do most of the other thiol reagents tested, and because low initial reactant concentrations were used to slow the reaction still further, the reaction was slower than any other reaction with Ellman's reagent in this study. No effect due to the spectrometer uv light was seen. In a separate experiment Ellman's reagent (0.0040 g, 1.0×10^{-5} mol) was transferred to a 100-ml volumetric flask and the solution made up with a deaerated phosphate buffer containing 10^{-6} M EDTA at pH 7.0. A uv scan from 310 to 465 nm was taken to show that no Ellman's anion was present. The volumetric flask was closed and placed in a Rayonet reactor, and illuminated using nine 350-nm and seven 253.7-nm lamps for 3 days. At the end of this time, the contents of the flask were deep yellow and the flask was warm to the touch. A second uv scan from 310 to 465 nm showed that 34% of the Ellman's reagent had been hydrolyzed, and that a quantity of Ellman's anion had formed which was consistent with hydroxide ion reaction as the cause of disappearance of the Ellman's reagent. Since the stoichiometry of the reaction was compatible with this reaction and since the quantity of Ellman's reagent consumed was approximately that expected at this pH, we conclude that light has no major effect on the rate of this reaction.

Influence of Buffer Composition and Concentration on k_1^{obsd} for Reaction of 2-Mercaptoethanol with Ellman's Reagent. Reactions were carried out using standard conditions in phosphate and TEA buffers at pH 7.0 [buffer, buffer concentration (M), k_1^{obsd} $\times 10^{-2}$ M^{-1} s^{-1}): phosphate, 0.05, 6.59; phosphate, 0.10, 8.00; phosphate, 0.20, 9.47; TEA, 0.05, 5.01; TEA, 0.10, 6.26; TEA, 0.20, 7.51. The ionic strength was held constant at 0.2 M in these reactions with KCl.

Determination of Thiol pK_a Values. Since the pK_a values of the dithiols differed by less than 2 units, their titration curves overlapped. Titration curves were obtained under argon with careful exclusion of atmospheric carbon dioxide, using 0.143 M carbonate-free potassium hydroxide solution.[23] Dilute solutions of thiols were used (0.001 M), so that activity corrections were not required. The KOH required to neutralize the thiol was added in 20 equal portions, and the pH of the solution measured 1 min after each addition. The pH meter was standardized against pH 7.00 and 10.00 Mallinckrodt BuffAR solutions. Analysis of the data followed a literature procedure,[24] using a computer program written for that purpose.[22]

Registry No.—Ellman's reagent, 69-78-3; thiolacetic acid, 507-09-5; 1,2:3,4-diepoxybutane, 1464-53-5; *threo*-1,4-dimercaptoacetyl-2,3-butanediol, 3483-12-3; *erythro*-1,4-dimercaptoacetyl-2,3-butanediol, 6892-68-8; 2,9-diaza-5,6-dithiacyclononanone, 60633-87-6; urea, 57-13-6; cystamine 2 HCl, 56-17-7; lead acetate,

301-04-2; 2-mercaptoethanol, 60-24-2; lead 2,2′-dithiodiethylurea, 60633-88-7; thioglycolic acid hydrazide, 760-30-5; thioglycolic acid methyl ester, 2365-48-2.

References and Notes

(1) Supported by the National Science Foundation (RANN, Grant G1 3428). Abbreviations used are: DTT, dithiotheitol; DTE, dithioerythreitol; EllS-SEll, Ellman's reagent, 5,5′-dithiobis(2-nitrobenzoic acid); EllS⁻, "Ellman's anion", the conjugate dianion of 2-nitro-5-thiobenzoic acid; CysSH, cysteine (or the cysteine moiety of a protein).
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A Simple, Empirical Function Describing the Reaction Profile, and Some Applications

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A simple, algebraic function is derived to represent the reaction profile of a concerted (one-step) reaction: $E = ax^4 + bx^3 - (4a + 3b)x^2/2$, where x is the reaction coordinate. It is shown that this function is in accord with the Hammond postulate and the Polanyi principle. It is used to evaluate the magnitude of the pressure-induced shifts of the transition state predicted by Walling several years ago, and to question the validity of a recent claim of the experimental verification of this effect. Further examination of this pressure effect leads to additional possibilities; among these are the vanishing of activation energies, the creation of certain new intermediates, and the conversion of degenerate sets of rapidly equilibrating structures into resonance hybrids.

The reaction profile showing how the energy of reacting molecules varies as they traverse the reaction coordinate has become a popular pedagogical device. The reason for this is that by means of it, one can conveniently illustrate a multitude of mechanistic phenomena. Concerted vs. stepwise reactions, intermediates vs. transition states, consecutive vs. competing reactions, early vs. late transition states, reversible vs. irreversible reactions, all these can be instantly indicated by means of the familiar curves one finds wherever mechanistically inclined chemists communicate with one another.

On a recent occasion we wished to make a quantitative estimate of pressure induced shifts of the transition state (vide infra), and discovered that none of the books exhibiting these curves records a function representing them.[2] We wish to describe an empirical function here for a simple, single-step reaction. We note its utility by showing, for example, that it behaves in the fashion demanded by the Hammond postulate and the Polanyi principle, and finally employ it to make the estimate referred to above.

The Function and Some of Its Features. We begin by noting that the general quartic

$$E = ax^4 + bx^3 + cx^2 + dx + e$$

is the simplest algebraic function which can have the general features of the reaction profile: a maximum flanked by two minima. E is the potential energy, and we let x represent the "distance" along the reaction coordinate, expressed as a fraction of the total to be traversed between the initial and final states. If we specify that at extreme values of x, E must be positive ($a > 0$), that the curve must pass through the origin ($e = 0$), that it must have a minimum there ($d = 0$) and at $x = 1$ [$c = -(4a + 3b)/2$], we have as the basic function

$$E = ax^4 + bx^3 - \frac{4a + 3b}{2}x^2 \qquad (1)$$

Several possibilities are shown in Figure 1; these include reactions with equilibrium constants less than, equal to, or greater than one (curves II, III, and IV, respectively, if we ignore the difference between energy and free energy), as well as extreme cases I and V which are reactions without activation energy. Beside the extrema at $x = 0$ and $x = 1$ (these points will be denoted by x_0 and x_1, respectively), there is a third (at $x^{\mp}$) which represents the transition state; it is found by dividing

$$\frac{dE}{dx} = 4ax^3 + 3bx^2 - (4a + 3b)x = 0$$

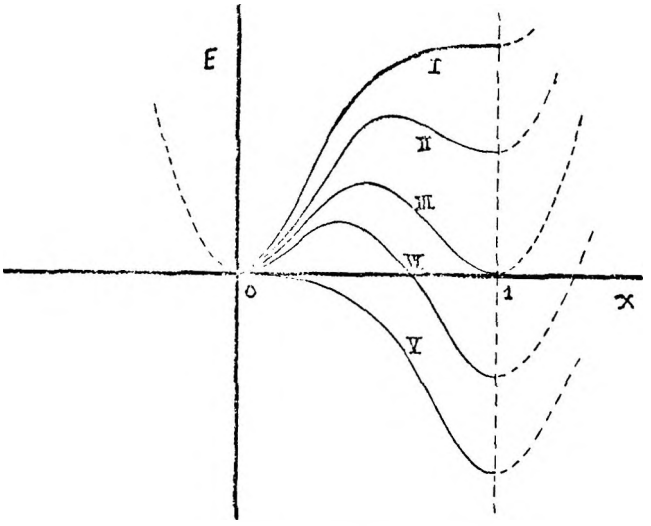


Figure 1. Various reaction profiles described by eq 1.

Table I. Characteristics of Several Curves in Figure 1

	Curve I	III	V
b/a	$-8/3$	-2	$-4/3$
Eq 1; E	$ax^4 - 8/3ax^3 + 2ax^2$	$ax^2(x-1)^2$	$ax^4 - 4/3ax^3$
E_1	$+1/3a$	0	$-1/3a$
$E^{\ddagger}$	$+1/3a$	$1/16a$	0
$x^{\ddagger}$	1	1/2	0
$x_{\text{infl.}}$	1/3; 1	$1/2 \pm 1/6\sqrt{3}$	0; 2/3
α_a[a]	1	1/2	0
α_b[a]	1	7/16	0

[a] See text below.

by $x(x-1)$, which gives

$$x^{\ddagger} = -\left(1 + \frac{3b}{4a}\right) \tag{2}$$

The corresponding activation energy $E^{\ddagger}$ is found by substitution of eq 2 into eq 1:

$$E^{\ddagger} = -a - b\left[\frac{5}{2} + \frac{9}{4}\left(\frac{b}{a}\right) + \frac{27}{32}\left(\frac{b}{a}\right)^2 + \frac{27}{256}\left(\frac{b}{a}\right)^3\right] \tag{3}$$

Similarly, the reaction energy

$$E_1 = -\left(a + \frac{1}{2}b\right) \tag{4}$$

Curves I and V are clearly the extreme cases at which the requirement of a vanishing first derivative at x_0 and x_1 still holds. Since in these two curves we also have a zero second derivative (at x_0 and x_1, respectively), we can obtain the limits of b from

$$\frac{d^2E}{dx^2} = 12ax^2 + 6bx - (4a + 3b) = 0$$

At x_1, $b/a = -8/3$; at x_0, $b/a = -4/3$. The pertinent data for curves I and V as well as those for the special case of $E_1 = 0$ (curve III) can now rapidly be deduced; they are summarized in Table I. It may be noted that since a is positive, b is negative. The more common types II and IV of course have intermediate values for b/a; once these constants have been chosen one can rapidly determine the corresponding function (from eq 1), E_1 (from eq 4), $E^{\ddagger}$ (from eq 3), and $x^{\ddagger}$ (from eq 2). The reverse process of finding values of a and b appropriate for certain values of E_1, $E^{\ddagger}$, and $x^{\ddagger}$ is also possible, but if $E^{\ddagger}$ is one of the two data specified, the complexity of eq 3 makes this process somewhat cumbersome.

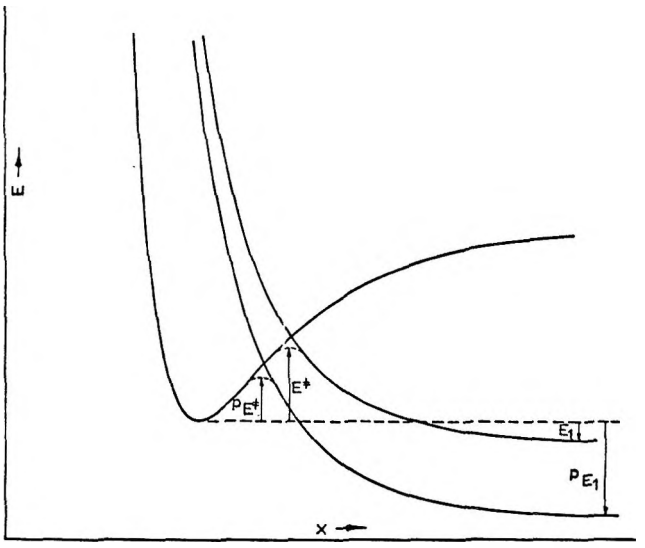


Figure 2. Reaction profiles of two displacement reactions XR + Y (Y′) according to Polanyi et al. (ref 6 and 7).

Applications. 1. The Hammond Postulate. This rule was recently discussed by Farcasiu.[3] The original statement by Hammond[4] is that if two states occurring consecutively during a reaction process have similar energies, they will have similar structures; but most chemists are probably more familiar with the corollary due to Melander,[5] who essentially derived the statement that for a given type of reaction, increased exothermicities imply earlier transition states. For our present purpose, we consider the energy of the starting material zero and relate the structure of the transition state $x^{\ddagger}$ to $E^{\ddagger}$ and E_1. From Figure 1 and Table I it is clear that the Hammond postulate is obeyed in the extremes; we now examine whether it applies at any intermediate value of $x^{\ddagger}$. We wish to show that for any given value of $E^{\ddagger}$, $x^{\ddagger}$ increases as E_1 increases; in other words

$$\left(\frac{\partial x^{\ddagger}}{\partial E_1}\right)_{E^{\ddagger}} > 0$$

Elimination of b/a between eq 2–4 leads to

$$E_1 = E^{\ddagger}\frac{(1 - 2x^{\ddagger})}{(x^{\ddagger} - 2)}\left(\frac{1}{x^{\ddagger}}\right)^3$$

Hence

$$\left(\frac{\partial x^{\ddagger}}{\partial E_1}\right)_{E^{\ddagger}} = \frac{\{x^{\ddagger 3}(x^{\ddagger} - 2)\}^2}{x^{\ddagger 3}(x^{\ddagger} - 2)(-2) - (1 - 2x^{\ddagger})(4x^{\ddagger 3} - 6x^{\ddagger 2})}\Big/E^{\ddagger}$$

$$= \left[\frac{x^{\ddagger 2}(x^{\ddagger} - 2)}{(x^{\ddagger} - 1)}\right]^2\Big/6E^{\ddagger}$$

which is clearly positive since $E^{\ddagger} > 0$.

2. The Polanyi Principle. Horiuti and Polanyi[6] considered reaction profiles as the resultants of attractive and repulsive potential energy curves (see Figure 2). Their analysis, initially applied to ionic displacement reactions, clearly implied a correlation between $E^{\ddagger}$ and E_1. In time the generalized proposition that in a series of closely related reactions greater product stability meant proportionately faster reaction and vice versa became one of the cornerstones of mechanistic chemistry:

$$E^{\ddagger} = \alpha E_1$$

or

$$\frac{\partial E^{\ddagger}}{\partial E_1} = \alpha$$

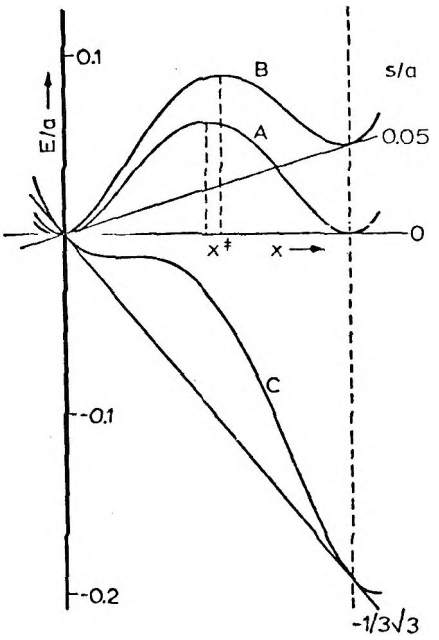


Figure 3. Pressure induced transition state progression.

Polanyi et al.[6] suggested that the proportionality factor α is about ½, but Evans[8] later concluded that it could be as low as ⅓. A relation of this sort can be derived from eq 1. Thus, if we eliminate b/a between eq 3 and 4, we obtain

$$\frac{E^{\ddagger}}{a} = -1 + 2\left(\frac{E_1}{a}+1\right)\left\{\frac{5}{2} - \frac{9}{2}\left(\frac{E_1}{a}+1\right) + \frac{27}{8}\left(\frac{E_1}{a}+1\right)^2 - \frac{27}{32}\left(\frac{E_1}{a}+1\right)^3\right\}$$

Then the derivative

$$\alpha_a = \left(\frac{\partial E^{\ddagger}}{\partial E}\right)_a = 5 - 18\left(\frac{E_1}{a}+1\right) + \frac{81}{4}\left(\frac{E_1}{a}+1\right)^2 - \frac{27}{4}\left(\frac{E_1}{a}+1\right)^3$$

$$= 5 + 9\frac{b}{a} + \frac{81}{16}\left(\frac{b}{a}\right)^2 + \frac{27}{32}\left(\frac{b}{a}\right)^3$$

Similarly

$$\alpha_b = 1 - \frac{9}{4}\left(\frac{b}{a}\right)^2 - \frac{27}{16}\left(\frac{b}{a}\right)^3 + \frac{81}{256}\left(\frac{b}{a}\right)^4$$

Both factors reach a maximum of +1 for curve I and a minimum of 0 for curve V. Throughout the intermediate region, α is positive, as can be shown, for example, from

$$\frac{d\alpha_a}{d(b/a)} = 9 + \frac{81}{8}\left(\frac{b}{a}\right) + \frac{81}{32}\left(\frac{b}{a}\right)^2 = 0$$

which has roots of $(b/a) = -4/3$ and $-8/3$ (note Table I). For curve III, α_a has the value ½, and it is equal to ⅓ for $b/a = -1.8493$.[9]

3. Pressure Induced Shifts in the Transition State. Since the absolute value of the activation volume is rarely more than 30 cm³/mol or so and since 1 cm³ atm is only 2.4×10^{-5} kcal, the $p\Delta V^{\ddagger}$ term is a vanishingly small part of $\Delta H^{\ddagger}$ or $\Delta G^{\ddagger}$ in reactions carried out under room conditions; however, at high pressures (e.g., 10 kbar ≈ 10^4 atm) the work term is no longer negligible. As was pointed out by Walling in 1963[10] and supported by Hamann[11] in 1964, this may in fact have the effect of shifting the position of the transition state, as is shown in Figure 3 (curve B). This illustrates a reaction with a positive activation volume and reaction volume carried out under high pressure; it is subject to a $p\Delta V$ term of increasing magnitude as the reaction coordinate is traversed. This additional term raises the entire curve above where it would be at zero pressure (A), and the maximum shifts somewhat to larger x. Thus, pressure in such a case has the effect of bringing about a later transition state.

It is perhaps unfortunate that this proposal came as a part of polemics centered on the question of whether the thermodynamic compressibility $(-1/V)(\partial V/\partial p)_T$ of a transition state might be adequately expressed by the Tait equation or not.[12] Walling's proposal led to such terms as "abnormal compressibility"[10] and "negative compressibility"[11] of transition states; furthermore, in their critical assessment of the magnitude of the effect, Benson and Berson[13] used a model involving the compression of a very weak bond, which may suggest that shifts of the transition state would necessarily be in the direction of a shorter bond. It seems preferable to the present authors to refer to Walling's phenomenon as a pressure induced progression of the transition state. The opposite phenomenon, occurring in cases of a monotonic volume decrease, would be retrogression of the transition state.

In the following discussion, the activation volume $\Delta V^{\ddagger} = V^{\ddagger} - V_0$, the reaction volume $\Delta V_1 = V_1 - V_0$, and $\Delta V = V_x - V_0$. Equation 1 allows us to make an estimate of the magnitude of the effect. If we assume for the moment that the work term obeys

$$w = p\Delta V \approx sx$$

then the enthalpy becomes

$$H = ax^4 + bx^3 - \frac{4a+3b}{2}x^2 + sx$$

and the slope is

$$\frac{dH}{dx} = 4ax^3 + 3bx^2 - (4a+3b)x + s$$

The three roots of this equation will ordinarily be real, and can rapidly be evaluated by the trigonometric method of solving cubics. One of them represents the new value of $x^{\ddagger}$, which will be denoted by ${}^{p}x^{\ddagger}$. The others give the new values of ${}^{p}x_0$ and ${}^{p}x_1$.

The solution of a cubic is too complicated to permit the writing of a general expression for the exact shift of $x^{\ddagger}$ as a function of a, b, and s; however, a few numerical examples may suffice. For the special case that $E_1 = 0$ at atmospheric pressure, for instance, if we have $E^{\ddagger} \approx 22.5$ kcal/mol, so that $a = 360$ kcal/mol[1], $b = -720$ kcal/mol, and $\Delta V_1 = 45$ cm³/mol (such values may be encountered in reverse Diels–Alder reactions, for example[14]), then the value of s at $p = 10$ kbar is 10.75 kcal/mol and the points of minimum and maximum enthalpy are the roots of

$$4x^3 - 6x^2 + 2x + 0.03 = 0$$

The solutions are ${}^{p}x_0 = -0.0144$, ${}^{p}x^{\ddagger} = 0.5301$, and ${}^{p}x_1 = 0.9843$. Thus a shift of $100[(0.5301 + 0.0144)/(0.9843 + 0.0144) - 0.5000]/0.5000 = 9.0\%$ would occur in the location of the transition state relative to the initial state. A slightly less accurate but more convenient procedure is to make use of a Taylor series expansion of the enthalpy:

$$H - H^{\ddagger} = \frac{dH}{dx}\delta x + \frac{1}{2}\frac{d^2H}{dx^2}(\delta x)^2 + \frac{1}{6}\frac{d^3H}{dx^3}(\delta x)^3 - - - - + s\delta x$$

where $\delta x = x - x^{\ddagger}$. Near the transition state, the first term vanishes, as does the derivative

$$\frac{d(H - H^{\ddagger})}{d(\delta x)} = 0 \approx \frac{d^2H}{dx^2}\delta x + s$$

Hence

$$\delta x \approx \frac{-s}{12ax^2 + 6bx - 4a - 3b}$$

For $x = \frac{1}{2}$, $b/a = -2$, one finds

$$\delta x \approx s/a = 0.0300$$

so that $x^{\ddagger}$ shifts to ${}^{p}x^{\ddagger} = 0.5300$. This value and the new values of ${}^{p}x_0$ and ${}^{p}x_1$ agree to three decimal places with those obtained by exact solution of the cubic equation.

The use of $w = sx$ is of course arbitrary. An especially simple solution is available if we replace it by a pressure contribution

$$w = r\left(x^3 - \frac{3}{2}x^2\right)$$

This curve—like the reaction profile itself—has been designed to have zero slope at x_0 and x_1, so that it will produce no changes in x at either extremity (see Figure 4). The constant r is defined by $H_1 = s = r(1 - \frac{3}{2})$, and so we may rewrite the pressure contribution as

$$w = -2sx^3 + 3sx^2 \qquad (5)$$

Now the enthalpy

$$H = ax^4 + (b - 2s)x^3 + \left(3s - \frac{4a + 3b}{2}\right)x^2$$

has a slope

$$\frac{dH}{dx} = 4ax^3 + (3b - 6s)x^2 + (6s - 4a - 3b)x$$

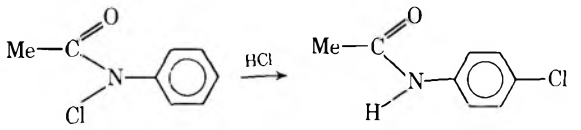
which equals zero at x_0, x_1, and at

$${}^{p}x^{\ddagger} = -\left(1 + \frac{3b}{4a}\right) + \frac{3s}{2a}$$

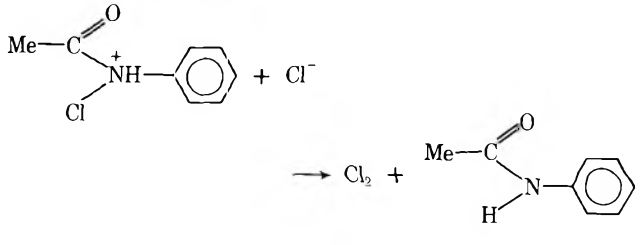
The shift in $x^{\ddagger}$ therefore now simply equals $3s/2a$, = 0.0450, or 9.0%.

However the shifts are evaluated, they are not very large. For instance, if we examine the effect of using $E_1 = -7.2$ kcal/mol ($a = 414$ and $b = -813.6$ kcal/mol), the shift in $x^{\ddagger}$ is now from 0.474 to 0.500; if E_1 is taken as -22.5 kcal/mol ($a = 522$ and $b = -999$ kcal/mol), then $x^{\ddagger}$ changes from 0.435 to 0.456. Very large shifts can of course be designed by assuming ever larger values of $p\Delta V^{\ddagger}$ and $p\Delta V_1$; however, it should be remembered that volume differences are not independent of pressure, and they invariably become smaller as the pressure is raised. It is quite common for $|\Delta V^{\ddagger}|$ to change, say, from 30 cm^3/mol at atmospheric pressure to 10 cm^3/mol at 5 kbar, and even less than that at still higher pressures. The assumption made above (of $\Delta V_1 = 2\Delta V^{\ddagger} = 45$ cm^3/mol *at 10 kbar*) is already so generous as to strain credulity, and still larger estimates have simply no counterpart in reality (except for some reactions of macromolecules). Further controlled increases in pressure are eventually ruled out for various experimental reasons.

One claim for a shift of this sort has been made to date. Fujii[15] has mentioned it in a recent paper describing a study of the Orton rearrangement in water containing up to 16 wt % ethanol:



The rate-determining step is



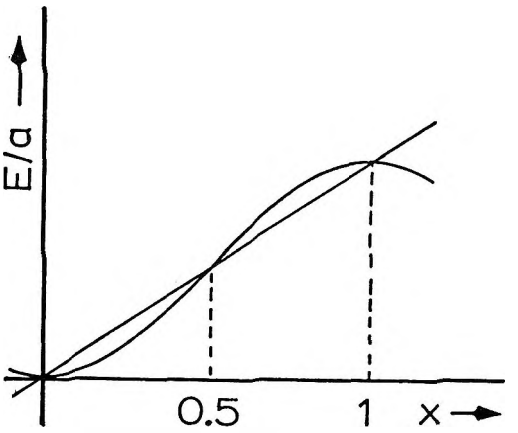


Figure 4. Equation 5: The straight line $w = sx$ is given for comparison; the integrated areas under the curves from x_0 and x_1 are the same.

The author used the relation between ln k and the dielectric constant D (Scatchard's equation)[16] to calculate $r_{N^+\cdots Cl^-}$; the necessary variation in D was achieved by applying changes in solvent composition. Since the change in D with pressure for these media is unknown, the Owen–Brinkley equation[17] was used to calculate it. The result was a change in r from 2.6 to 3.6 Å over a range of a mere 2 kbar, and this result was considered to confirm the operation of the Walling effect. However, the change seems far too large, especially if the modest pressure range and activation volume (+5 cm^3/mol) are considered; furthermore, since the ionic and van der Waals radii of chlorine are 1.80 Å, and the covalent radii of chlorine and nitrogen are about 1.0 and 0.7 Å, respectively, it is hard to see how the distance between the ionic centers could be much less than 3.7–4.7 Å at any stage, unless we assume that the rate-limiting step is a front-side displacement (at chlorine by chloride). It seems likely that the observation is a manifestation of the special solvent effects that are known[18] to operate in highly aqueous organic media, and which were not considered. As may be obvious from the discussion here, the Walling effect is going to be small even under the most favorable circumstances, and hence difficult to demonstrate; perhaps pressure sensitivity of the chlorine (35/37) isotope effect will be the method of choice.

An interesting phenomenon may be encountered if reactions of low $E^{\ddagger}$ and large, negative $\Delta V^{\ddagger}$ are studied at high pressures. We illustrate this by means of the symmetrical curve III. At the inflection points, the energy is $(\frac{1}{36})a$, and the slope reaches maxima there of $\pm(\frac{1}{9})a\sqrt{3}$. Since $E^{\ddagger}$ is $(\frac{1}{16})a$, one can readily show that the transition state vanishes altogether if $E^{\ddagger} < -(\frac{3}{16})s\sqrt{3}$. Thus, if $\Delta V^{\ddagger} = -22.5$ cm^3/mol and $\Delta V_1 = -45$ cm^3/mol at 10 kbar, in a reaction of activation energy less than 3.5 kcal/mol at atmospheric pressure, the starting material would pass over into product without having to pass a barrier at all at 10 kbar (see curve C of Figure 3). A phenomenon of this sort has been alluded to by Libby.[19]

Finally, it may be noted that it is not necessary that ΔV vary monotonically along the reaction coordinates; it may exhibit extremum behavior as does E itself.[10] Displacement reactions involving no net change of charge, and Diels–Alder reactions involving secondary orbital interactions, are examples of reactions in which $\Delta V^{\ddagger}$ is more negative than ΔV_1. In such reactions, as Figure 5 demonstrates, the addition of E and $p\Delta V$ may lead to a new minimum. In fact, by working at high pressure, we would have stabilized a transition state to the point that it is a reactive intermediate instead. In the displacement example, this might be a molecule containing a pentacovalent carbon atom, or an ion triplet; in the Diels–Alder reaction, a diradical would be indicated. A particularly

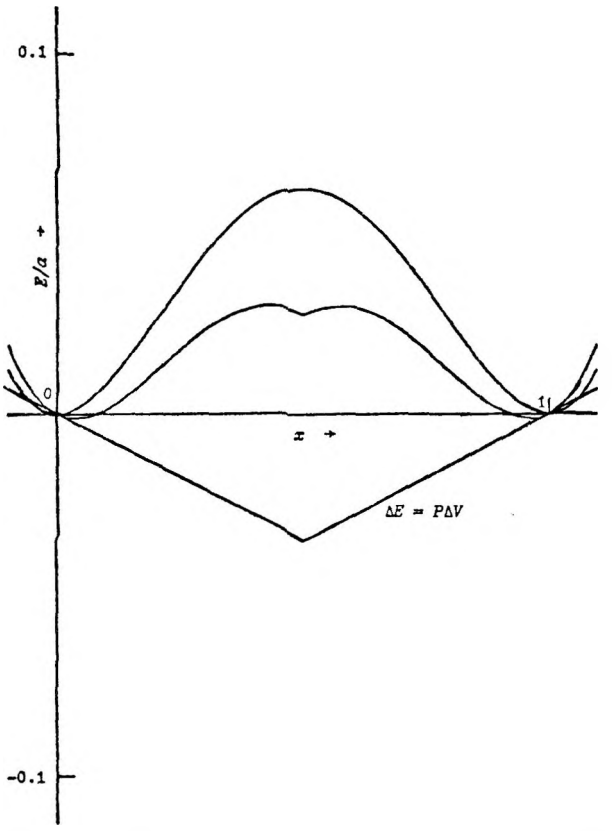
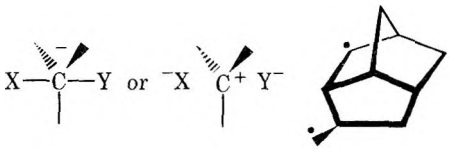


Figure 5. The pressure induced creation of an unstable intermediate.



interesting case would be the application of very high pressures to rapidly equilibrating valence isomers such as semibullvalene.[20] The activation energy for the degenerate isomerization is only a few kcal/mol; the [3,3] sigmatropic shift is characterized by a negative activation volume and a minimum *in the pressure profile.*[21] *Conversion into a pressure stabilized* resonance hybrid (sought by means of substituents in recent years[22]) is thus conceivable.

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References and Notes

(1) (a) At Stony Brook. (b) Molecular Dynamics Fellow at Stony Brook, 1974–1975; correspondence to this author should be addressed to 201 Service Memorial Institute, University of Wisconsin, Madison, Wis. 53706. (c) At Melbourne.
(2) The Eckart potential is an exception; see J. Eckart, *Phys. Rev.*, **35**, 1305 (1930). Its principal virtue has been the fact that its substitution into the wave equation gives a differential equation which can readily be integrated. The solution has been useful in theoretical analyses of tunnelling: J. J. Weiss, *J. Chem. Phys.*, **41**, 1120 (1964). The authors are indebted to an unknown referee for acquainting them with this literature. The Manning potential has been used in the analysis of the ammonia inversion; see M. F. Manning, *J. Chem. Phys.*, **3**, 136 (1935).
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(8) Reference 7, p 735.
(9) It may be noted here in passing that eq 1 may also be used to relate resonance energies with conventional structures. In this application, a is negative and *b* has values between $-(4/3)a$ and $-(8/3)a$, so that the curves, now the *mirror* images of those in Figure 2, lie below the *x* axis; $x^{\ddagger}$ now represents the "resemblance" of the hybrid with the contributing structures x_0 and x_1; the resonance energy is the difference between E_0 or E_1 (whichever is lower) and $E^{\ddagger}$. It should at once be obvious that $x^{\ddagger}$ will be closest to the canonical structure of lowest energy; if E_1 is also zero, the hybrid is exactly intermediate and the resonance energy reaches a maximum.
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Ferric Chloride in Ether. A Convenient Reagent for the Conversion of Epoxides into Chlorohydrins

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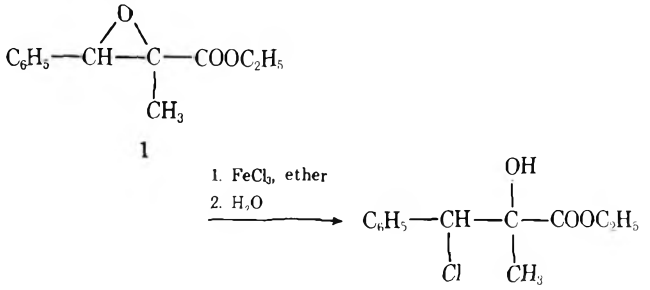
During a study of the photochemistry of glycidic esters in the presence of metallic salts, a reaction of ethyl (*Z*)-2-methyl-3-phenylglycidate (*Z*-1) with an equimolar amount of $FeCl_3$ in ether was observed to take place rapidly at room temperature in the dark. After 2 min the ether solution was washed with water and found to give a mixture of *threo*- and *erythro*-ethyl 2-methyl-3-chloro-3-phenyllactate (2) in 82%



yield,[1] uncontaminated by starting material or rearrangement products.

The reaction was stereoselective, yielding predominantly the product of back-side attack onto the benzylic carbon–oxygen bond. Thus, the ratio of *threo*- to *erythro*-**2** was 3.5:1 from *Z*-**1**, while it was 0.62:1 from *E*-**1** under the same conditions.

It is well known that the reaction of Lewis acids with epoxides may follow several paths: isomerization to carbonyl products, isomerization to allylic alcohols or derivatives, or reaction with nucleophiles.[2] In this last category, the formation of fluorohydrins and bromohydrins in reactions with boron trifluoride and magnesium bromide, respectively, are examples where the nucleophile is derived from the Lewis acid itself, but there are very few examples of chlorohydrins having been prepared by reaction of an epoxide with a metal chloride, and only one where ferric chloride was used for this conversion.[3] There, ethylene and propylene oxides were shown to give their chlorohydrins in 23 and 34% yield, respectively.

Before checking on the generality of the reaction of $FeCl_3$ in ether with other epoxides, the published reactions were repeated with similar results, and their complexity was confirmed by a GLC analysis which disclosed the presence of at least 28 products in the reaction with ethylene oxide. These were not investigated further.

Other examples of epoxides which were investigated are shown in Table I.

Cyclohexene oxide (**3**) yielded 2-chlorocyclohexanol which had NMR and ir spectra practically superimposable on those of the trans isomer obtained by hydrogen chloride treatment.[4] The trace of cis isomer was detected by GLC.

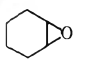
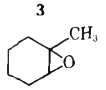
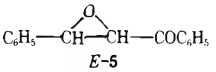
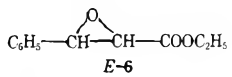
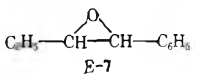
1-Methylcyclohexene oxide (**4**) was studied in order to compare its reaction with $FeCl_3$ to that with $MgBr_2$ which yielded carbonyl products exclusively, without any bromohydrins.[5] We found that although **4** reacted with $FeCl_3$ in ether to produce small amounts of aldehyde and ketonic materials (from NMR and ir analysis), a good yield of trans chlorohydrin was obtained. This product as well as that obtained by reaction of **4** with HCl was free from the cis isomer (GLC analysis).[6]

The stereoselectivity was not as good in the reaction of epoxides which were not part of a fused bicyclic system. Thus chalcone oxide [(*E*)-2-phenyl-3-benzoyloxirane, **5**] yielded a mixture of chlorohydrins which was nearly 50% produced by cis opening.[7] The major by-product of the reaction was 2-benzoylphenylacetaldehyde, the usual rearrangement product of this epoxide.[8] We note that in this case both the yield of chlorohydrins and the stereoselectivity of the reaction were not as high as reported in the treatment with $SnCl_4$.[8]

Ethyl (*E*)-2-phenylglycidate (**6**) reacted almost identically with $FeCl_3$ in ether and with HCl in ether, in terms of yield and stereoselectivity.

Finally, (*E*)-stilbene oxide (**7**) gave quantitative isomer-

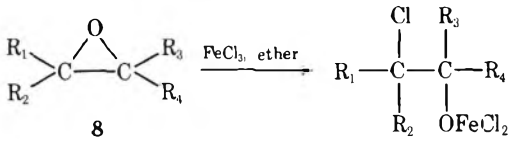
Table I. Reaction of Ferric Chloride in Ether with Selected Epoxides

Substrate	Registry no.	Yield of chlorohydrin (isolated)	% cis opening
 **3**	279-49-2	78 (6628-80-4)[b]	6 (17002-09-4)[b]
 **4**	1713-33-3	74 (60537-96-4)[b]	0
 *E*-**5**	7570-86-7	55 (22464-01-3)[b]	50 (22464-02-4)[b]
 *E*-**6**	2272-55-1	64[a] (60537-97-5)[b]	33 (60537-98-6)[b]
 *E*-**7**	1439-07-2	0	

[a] Estimated from NMR. [b] Registry no.

ization to diphenylacetaldehyde, even though an independent treatment of the expected chlorohydrin showed it to be stable under the reaction conditions. In this case, it is likely that the phenyl migration took place concertedly with the epoxide ring opening, or (less probably) from an organoiron derivative of the chlorohydrin itself.[9]

In all this work, we made no attempts to characterize the intermediate organoiron compounds produced in the reactions, which we formulate as **8** by analogy with the reaction of other metal halides with epoxides.[2]



8

Ether seemed to be the solvent of choice since **1** did not react with $FeCl_3$ in chlorobenzene, toluene, dimethyl sulfoxide, or when no solvent was used. In carbon tetrachloride, there was only 50% conversion after 25 min, while in acetonitrile the conversion was very slow, yielding 30% of **2** after 16 h. In methanol, the solvent participated in the reaction, and *Z*-**1** gave *threo*-3-methoxy-3-phenyllactate stereospecifically in 30% yield after 20 h. Under the same conditions, there was no reaction with the *E* isomer. Benzene gave mixed results: $FeCl_3$ is appreciably soluble in this solvent, and the conversion of *Z*-**1** to **2** took place readily with good stereoselectivity (66% threo). However, **4** did not yield any chlorohydrins in these conditions, and instead isomerized quantitatively into 2-methylcyclohexanone, a reaction reminiscent of that described with $MgBr_2$ in ether.[5]

The high solubility of $FeCl_3$ in ether containing hydrogen chloride has been used for the selective extraction of this salt from aqueous solutions,[10] and the crystalline mono- and dietherates of $HFeCl_4$ were prepared from such ether solutions.[11] Similarly, the preparation of a mono-[11,12] and a dietherate[11] of $FeCl_3$ itself has been claimed, but the physical properties of these compounds were barely described. However, the monoetherate obtained by concentration of a solution of $FeCl_3$ in ether was reported to be soluble in benzene.[12] We therefore attempted to use such a solution for preparing **2** from **1**. Here the conversion took place smoothly at room temperature, but without stereoselectivity.

The reaction of **4** with ferric chloride etherate in benzene yielded a mixture of the isomeric 1-methylcyclopentanecarboxaldehyde (33%) and 2-methylcyclohexanone (66%), while it gave a mixture of the chlorohydrin (50%), the aldehyde (26%), and the ketone (24%) with ferric chloride etherate in carbon tetrachloride.

We also observed that benzene provided no improvement over ether in the reaction of **7** with ferric chloride etherate. Complete rearrangement to diphenylacetaldehyde also took place.

Finally, the superior solvent power of isopropyl ether over ethyl ether for $FeCl_3$[12] suggested the use of that solvent as a possible improvement in the procedure. However, when treated with $FeCl_3$ in isopropyl ether, *Z*-**1** could be recovered quantitatively.

In conclusion, although $FeCl_3$ or its etherate(s) may be occasionaly used in other solvents, no combination proved superior to $FeCl_3$ in ether, which is a very convenient, if not general, reagent for synthesizing chlorohydrins from epoxides.[14]

Experimental Section

Representative Reaction of an Epoxide with Ferric Chloride in Ether. Anhydrous $FeCl_3$ (150 mg, 0.73 mmol) was dissolved in 50 ml of anhydrous ether. The reaction was exothermic, and produced an orange solution, to which 150 mg (0.73 mmol) of **1** was added. After 2 min of stirring, the green-black solution was diluted with 25 ml of ether and washed with two 50-ml portions of water. The aqueous extracts were combined and extracted with 50 ml of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated under vacuum, and yielded 145 mg (0.60 mmol, 82% yield) of a slightly yellow liquid which crystallized slowly. The solid melted at 45–70 °C: mass spectrum *m/e* 242 (M^+), 206, 190, 11/, 116, 115, 105, and 91; NMR ($CDCl_3$) 1.15 (t, J = 7 Hz, 3 H), 1.60 (s, 3 H), 4.05 (q, J = 7 Hz, 2 H), and 5.07 ppm (s, 1 H) for the erythro (22.5%), and 1.18 (s, 3), 1.32 (t, J = 7 Hz, 3 *H*), 4.30 (q, J = 7 Hz, 2 *H*), and 5.12 ppm (s, 1 *H*) for the threo isomer (77.5%). The aromatic signals were centered at 7.32 ppm (m, 5 H), and the hydroxyls at 3.30 ppm (disappearing in the presence of D_2O) for both diastereoisomers.[18]

Registry No.—*E*-**1**, 7141-24-4; *z*-**1**, 7042-28-6; *threo*-**2**, 59069-85-1; *erythro*-**2**, 59069-84-0; $FeCl_3$, 7705-08-0.

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(2) General references may be found in (a) F. Johnson in "Friedel-Crafts and Related Reactions", Vol. IV, G. A Olah, Ed., Interscience, New York, N.Y., 1965, p 1; (b) M. S. Malinovskii, "Epoxides and Their Derivatives", Israel Program for Scientific Translation, 1965; (c) G. Dittus in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 6/3, Georg Thieme Verlag, Stuttgart, 1955, p 437.
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(6) The synthesis of both chlorohydrins was described by H. Bodot, J. Jullien, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 1097 (1958). The trans isomer obtained by reaction of **4** with HCl in ether was believed to contain 45% of the cis isomer. This came from rate studies in the reaction of this product with base, assumed to convert the trans isomer quantitatively into **4**. Our GLC analysis showed the product of the HCl treatment to be pure trans, but its complete conversion into **4** in the presence of base was more sluggish than anticipated, thereby accounting for the discrepancy. The synthesis of the cis isomer was accomplished by these authors by reducing 2-chloro-2-methylcyclohexanone with $LiAlH_4$. We did not repeat this reaction and cannot confirm whether 19% of the trans isomer was indeed formed along with the cis chlorohydrin which melted at 19 °C. The reduction with $NaBH_4$ in ethanol yielded the cis isomer which contained ca. 7% of trans (GLC analysis), but the dehydrochlorination of this cis isomer (mostly to 2-methylcyclohexanone) took place at an appreciable rate under the published conditions, thus also invalidating this type of analysis. Our recrystallized cis chlorohydrin melted at 27 °C.
(7) We encountered some difficulties in the characterization of one of the chlorohydrins. Although pure by all spectroscopic criteria, it melted sharply at 90 °C, when 72 and 107 °C are the values reported for the two diastereoisomeric 1-benzoyl-2-chloro-2-phenylethanols.[8a] We later found that 90 °C was the melting point for a different crystalline modification of the compound which usually melts at 107 °C.
(8) (a) H. O. House, *J. Org. Chem.*, **21**, 1306 (1956); (b) *J. Am. Chem. Soc.*, **76**, 1235 (1954), and references cite, therein.
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(13) R. W. Dodson, G. J. Forney, and E. H. Swift, *J. Am. Chem. Soc.*, **58**, 2573 (1936).
(14) It is interesting to mention three other recent reports where $FeCl_3$ was also used for cleaving ethers. In one[15] $FeCl_3$ in acetic anhydride was shown to convert ethers into a mixture of acetates, while in the other $FeCl_3$ in dimethylformamide cleaved and oxidized the trimethylsilyl ethers of bicyclic cyclopropanols into β-chloro ketones.[16] Finally, the poorly defined $FeCl_3$–*n*-BuLi system was shown to deoxygenate epoxides into olefins.[17]
(15) B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).
(16) Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2078 (1976).
(17) T. Fujisawa, K. Sugimoto, and H. Ohta, *Chem. Lett.*, 883 (1974).
(18) Our limited experience suggests that it is not necessary to have complete solution of the $FeCl_3$ in ether prior to its reaction with an epoxide. The reagent dissolves rapidly as the reaction proceeds, and the total volume of solvent necessary for larger scale reactions may therefore be kept small.

Synthesis of 5-(*tert*-Alkyl)resorcinols

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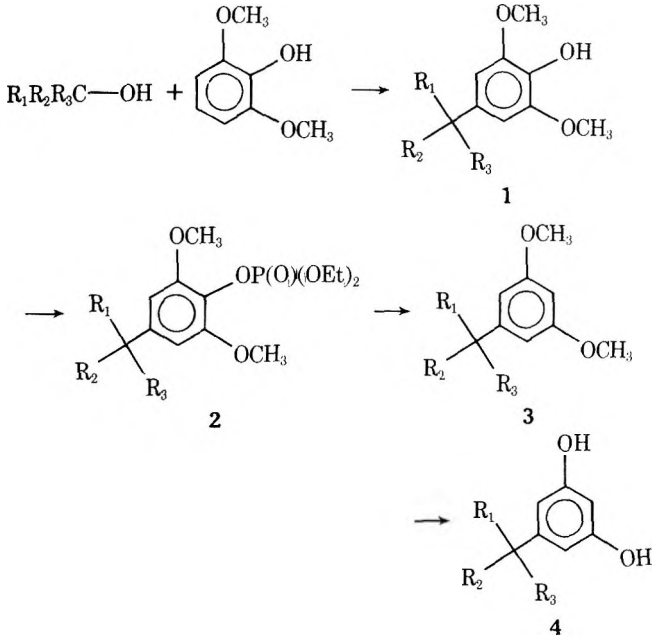
In connection with other work underway in these laboratories, a short and efficient method for the preparation of large

quantities of 5-(1,1-dimethylheptyl)resorcinol was required. Previous syntheses of this material, from 3,5-dimethoxybenzyl cyanide[1] and 3,5-dimethoxybenzonitrile,[2] have been devised but are somewhat lengthy and require relatively expensive starting materials. In recent years, numerous syntheses of 5-alkylresorcinols have appeared[3-12] but almost without exception these are applicable to the preparation of normal alkyl resorcinols only. A preparation of 5-*tert*-butylresorcinol has also appeared.[13]

Our synthesis is based upon the finding that alkylation of 2,6-dimethoxyphenol with tertiary carbonium ion precursors occurs predominantly, if not exclusively, para to the hydroxyl group. Thus, treatment of the dimethoxyphenol with 1,1-dimethyl-*n*-hexylcarbinol in methanesulfonic acid at 50 °C afforded a 98% crude yield of 5-(1,1-dimethylheptyl)-2,6-dimethoxyphenol which, without further purification,[14] was converted to a crystalline phosphate ester with diethyl phosphonate, carbon tetrachloride, and triethylamine in 75% yield. Treatment with Li/NH_3,[15] followed by demethylation of the product with boron tribromide, provided the crystalline resorcinol in 50–60% yield. The sequence has been successfully



carried out on a scale of several hundred grams with comparable yields, and has been applied to the preparation of some new resorcinols (see Table I, **4a–f**).

As can be seen from Table I, yields are generally excellent except for the last (demethylation) step. Boron tribromide was found to be the reagent of choice, other reagents (e.g., pyridine hydrochloride, methylmagnesium iodide) giving substantially poorer results. The alkylation step (i.e., preparation of **1**) could only be accomplished in high yield with sulfuric acid, but methanesulfonic acid gave cleaner reactions and easier purifications. Attempts to alkylate 2,6-dimethoxyphenol with oxygenated carbinols, e.g., $EtO(CH_2)_2C(CH_3)_2OH$, gave only decomposition products.

Experimental Section

Melting points are uncorrected. Chromatographic purifications were performed on columns of Woelm silica gel, activity 1. The tertiary carbinols were prepared and purified by standard methods. A representative procedure follows.

4-(1′,1′-Dimethylheptyl)-2,6-dimethoxyphenol (1a). A mixture of 15.4 g (0.10 mol) of 1,1-dimethyl-1-heptanol, 15.49 (0.10 mol) of 2,6-dimethoxyphenol, and 20 ml of technical methanesulfonic acid was stirred at 50 °C for 3 h and then at room temperature overnight. The mixture was poured onto ice and extracted with methylene chloride. The extracts were washed with H_2O and saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to afford 27.4 g (98%) of an oil used directly in the next step.

Table I

Compd	R_1	R_2	R_3	% yields[a] 1	2	3	4
a	CH_3	CH_3	n-C_6H_{13}	98	70	95	85
b	CH_3	CH_3	C_6H_5	98	98	86	67[b]
c	CH_3	CH_3		92	74	87	60[b]
d	CH_3	C_6H_5	n-C_6H_{13}	99	75	92	45[b]
e	CH_3	CH_3		98	76	92	17[b]
f				85	100	85	70

[a] Crude yields; purified yields generally 10–15% lower. [b] After chromatography.

4-(1′,1′-Dimethylheptyl)-2,6-dimethoxyphenyl Diethylphosphate (2a). A solution of 35.9 g (0.128 mol) of crude **1a** in 20 ml of CCl_4 was stirred and cooled in an ice bath. Diethyl phosphonate (19.4 ml, 0.15 mol) was added, followed by dropwise addition of 20.8 ml (15.2 g, 0.15 mol) of triethylamine. The mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The mixture was then diluted with 20 ml of methylene chloride, washed (H_2O, 4 N NaOH, H_2O, 1 N HCl, H_2O, saturated NaCl), filtered to remove a trace of solid, and dried ($MgSO_4$). Removal of the solvent provided a residue which upon crystallization from 100 ml of *n*-hexane afforded 37.0 g (70%) of needles: mp 61–64 °C; NMR ($CDCl_3$) δ 6.55 (s, 2 H), 4.30 (2 q, 4 H), 3.85 (s, 6 H), 1.4 (t, 6 H), 1.25 (s, 6 H), 1.8–0.5 (m, 13 H).

1-(1′,1′-Dimethylheptyl)-3,5-dimethoxybenzene (3a). A solution of 36.5 g (0.09 mol) of **2a** in 75 ml of Et_2O and 15 ml of THF was added dropwise to 200 ml of NH_3 as a total of 1.25 g (0.18 g-atom) of Li metal was added at a rate to maintain a blue color. After 1 h, excess Li was destroyed with NH_4Cl, the mixture was diluted with 100 ml of Et_2O, and the NH_3 was allowed to evaporate. The mixture was treated with H_2O and the layers separated. The Et_2O layer was washed (4 N, NaOH, H_2O, saturated NaCl), dried ($MgSO_4$), and evaporated to afford 22.1 g (95.4%) of **3a** as an oil which was purified chromatographically: NMR ($CDCl_3$) δ 6.45 (d, 2 H), 6.25 (t, 1 H), 3.75 (s, 6 H), 1.25 (s, 6 H), 1.8–0.5 (m, 13 H).

5-(1′,1′-Dimethylheptyl)resorcinol (4a). A solution of 26.4 g (0.10 mol) of **3a** in 100 ml of methylene chloride was added dropwise to a stirred, cold (ice bath) solution of 62.5 g (0.25 mol) of boron tribromide in 200 ml of methylene chloride over 1 h. The reaction mixture was then stirred at 0 °C for 2 h and allowed to warm to room temperature overnight. The mixture was then recooled to 0 °C and cautiously treated dropwise with H_2O (200 ml). The organic layer was separated and extracted thoroughly with 2 N NaOH. The NaOH extracts were acidified with 1 N HCl and the mixture extracted with Et_2O. The combined Et_2O extracts were washed with saturated NaCl, dried, and evaporated to provide 20.2 g (85%) of **4a**: mp 97–99 °C; NMR ($CDCl_3$) δ 6.35 (d, 2 H), 6.15 (t, 1 H), 5.2 (bs, 2 H, exchanges with D_2O), 1.20 (s, 6 H), 1.8–0.5 (m, 13 H).

Other resorcinols prepared: **4b**, mp 108–110 °C (C_6H_6–Skelly B); **4c**, mp 145–147 °C (EtOAc–hexane); **4d**, oil (purified by chromatography); **4e**, mp 125–127 °C (C_6H_6–Skelly B); **4f**, mp 284–285 °C (toluene–EtOAc).

Registry No.—**1a**, 60526-69-4; **1b**, 60526-70-7; **1c**, 60526-71-8; **1d**, 60526-72-9; **1e**, 60526-73-0; **1f**, 60526-74-1; **2a**, 60526-75-2; **2b**, 60526-76-3; **2c**, 60526-77-4; **2d**, 60526-78-5; **2e**, 60526-79-6; **2f**, 60526-80-9; **3a**, 60526-81-0; **3b**, 60526-82-1; **3c**, 60526-83-2; **3d**, 60526-84-3; **3e**, 60526-85-4; **3f**, 60526-86-5; **4a**, 56469-10-4; **4b**, 60526-87-6; **4c**, 60526-88-7; **4d**, 60526-89-8; **4e**, 60526-90-1; **4f**, 60526-91-2; 1,1-dimethyl-1-heptanol, 628-44-4; α,α-dimethylbenzenemethanol, 617-94-7; α,α-dimethylcyclohexanemethanol, 16664-07-6; α-hexyl-α-methylbenzenemethanol, 7252-61-1; α,α-dimethyltricyclo[3.3.1.1^{3,7}]decane-1-methanol, 775-64-4; tricyclo[3.3.1.1^{3,7}]decan-1-ol, 768-95-6; 2,6-dimethoxyphenol, 91-10-1.

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Generation of the Trans Enolate of Chloroacetaldehyde via a β-Oxido Carbenoid

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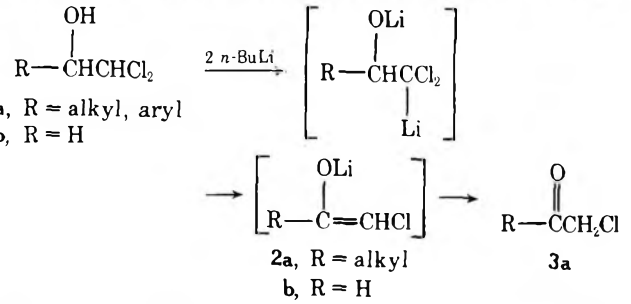
On treatment with 2 equiv of *n*-butyllithium, 1-substituted 2,2-dichloroethanols **1a** and related species undergo rearrangement via β-oxido carbenoids to afford ketones **3a** in high



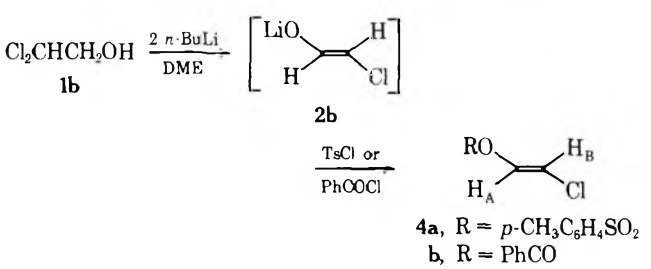
1a, R = alkyl, aryl
b, R = H

2a, R = alkyl
b, R = H

3a

yields.[1] *Although the chemistry of β-oxido carbenoids has* been intensively investigated by us[2] and others,[3] the stereochemistry of the double bond of the enolate anion **2** has not been elucidated. Investigation of the reaction of the parent compound, 2,2-dichloroethanol (**1b**), would give us not only information about the stereochemical outcome of this rearrangement, but also a way for the preparation of chloroacetaldehyde enolate (**2b**), a previously unknown enolate species.

We have found that 2 equiv of *n*-butyllithium effects rearrangement of 2,2-dichloroethanol (**1b**)[4] at −78 °C to give the lithium enolate of chloroacetaldehyde (**2b**). This enolate is subsequently allowed to react with *p*-toluenesulfonyl *chloride and is isolated as the O-tosylated derivative* **4a** in 86%



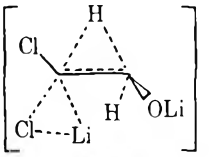
1b

2b

4a, R = *p*-$CH_3C_6H_4SO_2$
b, R = PhCO

yield. In addition, this rearrangement reaction gives exclusively the *E* isomer of the enol tosylate **4a** (vide infra). Although alcohols **1a** react rapidly (−50 °C, 30 min) with *n*-butyllithium,[2b] less than half of 2,2-dichloroethanol (**1b**) was consumed under the same conditions. At a higher temperature (−20 °C, 2 h) the yield of the enol tosylate **4a** was reduced to 58%, yet under the optimum conditions (−78 °C, 5 h), it reached the highest value of 86%. It is interesting that the enolate **2b** gives the O-tosylated derivative in high yield, and as a single isolable product, since the reaction of an enolate anion with arenesulfonyl chloride has long been known to afford mainly chlorinated products instead of sulfonylated products.[5]

In order to establish the stereochemistry of the enolate **2b**, the enolate **2b** was transformed to the corresponding enol benzoate **4b**, since a reliable stereochemical assignment by NMR spectroscopy is possible with enol ester derivatives.[6] The enolate **2b** generated in DME was treated with benzoyl chloride to give the expected enol benzoate **4b** in 56% yield. On NMR analysis the benzoate **4b** exhibited the same value of the coupling constant as the tosylate **4a**, i.e., J_{AB} = 11 Hz. A coupling constant between two vicinal protons attached to a disubstituted double bond is known to be closely related to the electronegativity of the substituents, and its magnitude is greatly reduced by both acyloxy and chloro groups.[6] Therefore, the value (J_{AB} = 11 Hz) of the enol benzoate **4b** should point out an *E* geometry of the double bond, and at the same time, the same geometry of the double bond of the lithium enolate **2b**.[7] With respect to the stereochemistry of the enolate **2b**, reactions at temperatures ranging from −100 to −20 °C uniformly gave the same result. An electronic repulsion in the transition state **6** is most likely the reason of the stereospecificity of this rearrangement.



6

Experimental Section

General. Melting points, which were determined in glass capillaries, and boiling points are uncorrected. Infrared spectra were obtained on a Hitachi EPI G3 spectrometer. NMR spectra were determined on a Varian Associates Model T-60 spectrometer and the chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were determined on a Hitachi RMU-7M spectrometer at Mass Spectral Laboratory, Tokyo Institute of Technology. Microanalyses were performed at Microanalytical Laboratory, Tokyo Institute of Technology.

(*E*)-2-Chloroethenyl 4-Toluenesulfonate (4a). 2,2-Dichloroethanol (114 mg, 1.00 mmol) in 5 ml of DME was treated with 1.55 M *n*-butyllithium in hexane (1.42 ml, 2.20 mmol) at −78 °C for 5 h. The resulting white suspension was treated with 197 mg of *p*-toluenesulfonyl chloride (1.00 mmol) dissolved in 2 ml of DME at −78 °C for 30 min and for 1 h at room temperature. The white reaction mixture was poured into 10 ml of water, and extracted with ether (10 ml × 3). The ethereal extract was dried ($MgSO_4$) and concentrated in vacuo to leave a yellow oil, which was homogeneous on TLC (R_f 0.45, benzene) and NMR analysis. Purification by preparative TLC gave the title tosylate **4a** (202 mg, 86%): bp 95–100 °C (bath temperature, 0.014 mm); ir (neat) 1600 (m), 1380 (s), 1195 (s), 1180 (s), 1070 (s), 890 cm^{-1} (m); NMR (CCl_4) δ 2.45 (s, 3 H, CH_3–), 6.00 (d, *J* = 11 Hz, 1 H, ClCH=C), 6.75 (d, *J* = 11 Hz, 1 H, OCH=C), 7.30 (unresolved d, *J* = 8 Hz, 2 H, aromatic protons ortho to methyl group), 7.70 (unresolved d, *J* = 8 Hz, 2 H, aromatic protons meta to methyl group); mass spectrum (70 eV) *m/e* (rel intensity) 232 and 234 ($M^{\cdot+}$), 155 (23), 91 (100), 65 (59), 63 (23), 51 (20), 49 (24), 39 (30).

Anal. Calcd for $C_9H_9O_3ClS$: C, 46.46; H, 3.90; S, 13.78. Found: C, 46.35; H, 3.95; S, 13.69.

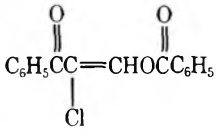
1-Benzoyloxy-2-chloro-(*E*)-ethene (4b). The DME (8 ml) solution of the lithium enolate **2b** which was prepared in the same manner as described above using 177 mg of 2,2-dichloroethanol (1.55 mmol) and 1.42 M *n*-butyllithium (2.18 ml, 3.10 mmol) was treated

at −78 °C with freshly distilled benzoyl chloride (218 mg, 1.55 mmol) in 2 ml of DME. After stirring for 30 min at −78 °C, the reaction mixture was allowed to warm to room temperature. The yellow mixture was subsequently poured into 10 ml of water, and extracted with ether (10 ml × 3). The extract was purified on preparative TLC to give two products, A and B.

A was the title compound **4b** (158 mg, 56%, R_f 0.5, benzene). Bulb-to-bulb distillation afforded an analytical sample which solidified on standing (mp 26–27 °): bp 65 °C (bath temperature, 0.015 mm); ir (neat) 1740 (s), 1640 (w), 1260 (s), 1130 cm^{-1} (s); NMR (CCl_4) δ 6.25 (d, J = 11 Hz, ClCH=C), 7.20–7.55 (m, 3 H, aromatic protons), 7.70 (d, J = 11 Hz, 1 H, OCH=C), 7.90–8.20 (m, 2 H, aromatic protons).

Anal. Calcd for $C_9H_7O_2Cl$: C, 59.20; H, 3.87. Found: C, 59.45; H, 3.97.

B was the doubly acylated product **7** (48 mg, 11%, R_f 0.25, benzene): mp 98.5–100 °C (hexane); ir (CCl_4) 1760 (s), 1730 (shoulder), 1675 (m), 1630 (m), 1600 (m), 1240 (vs), 1150 (vs), 1005 cm^{-1} (vs); NMR (CCl_4) δ 7.1–8.3 (m, 10 H), 8.45 (s, 1 H).



7

Anal. Calcd for $C_{16}H_{11}O_3Cl$: C, 67.01; H, 3.87. Found: C, 66.72; H, 3.97

Registry No.—**2b**, 60537-99-7; **4a**, 60538-00-3; **4b**, 60538-01-4; **7**, 60538-02-5; 2,2-dichloroethanol, 598-38-9; *p*-toluenesulfonyl chloride, 98-59-9; benzoyl chloride, 98-88-4.

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Dehydroaporphines. Dichlorocarbene Addition to Dehydronuciferine

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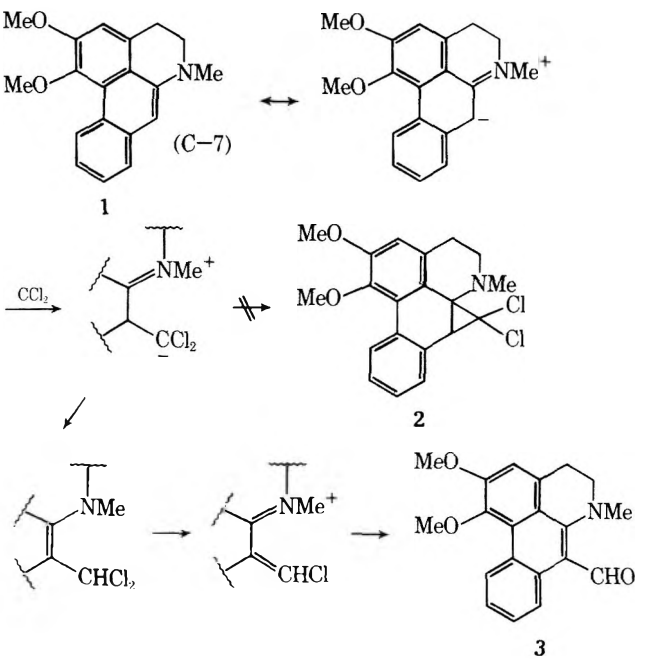
A recent protonation study of some representative dehydroaporphines has shown that protonation occurs readily at C-7, indicative of a certain degree of enamine-type character in dehydroaporphines.[1] This result suggested that the C-7 carbon of a dehydroaporphine might be sufficiently nucleophilic to allow the introduction of carbon substituents at this position, thus affording a route to a variety of hitherto unavailable but pharmacologically interesting 7-substituted aporphines. As part of a broad study of the scope and limitations of this idea, we now report the reaction of dichlorocarbene with dehydronuciferine (**1**), a typical dehydroaporphine.

It has been reported recently that dichlorocarbene adducts of olefins, including even phenanthrene, can be prepared conveniently and in high yield by the use of chloroform, aqueous sodium hydroxide, and a phase-transfer catalyst.[2] Under these conditions, dehydronuciferine (**1**) was cleanly converted into a single crystalline product, mp 161–163 °C. The composition and properties of this material showed that it was not the expected cyclopropane **2**, but rather dehydronuciferine-7-carboxaldehyde (**3**). In accord with this formulation, the infrared spectrum of **3** showed a conjugated carbonyl band at 6.24 μ. The NMR spectrum of **3** showed that the C-7 proton of dehydronuciferine (at δ 6.50) was replaced by a low-field aldehyde proton at δ 10.13; the *N*-methyl of **3** appeared at δ 3.30 as compared to δ 2.95 in dehydronuciferine, indicating a considerable deshielding effect of this methyl by the aldehyde group.



The formation of aldehyde **3** from dehydronuciferine can be rationalized by a mechanism analogous to that of the Reimer–Tiemann reaction, as illustrated below, the critical step being the attack of the electron-deficient CCl_2 by the nucleophilic C-7 carbon of the dehydroaporphine.

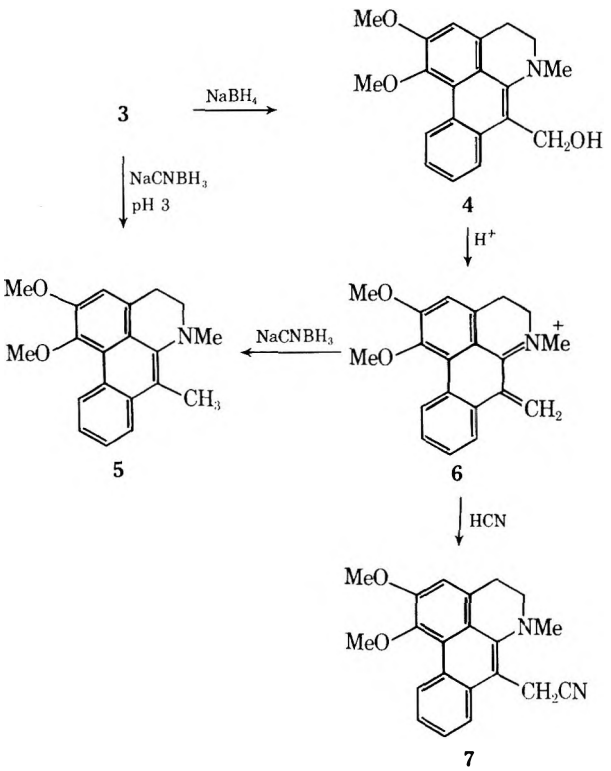
Reduction of aldehyde **3** with sodium cyanoborohydride at pH 3 afforded, in good yield, 7-methyldehydronuciferine (**5**), mp 99–100 °C. The uv spectrum of **5** was almost identical with that of dehydronuciferine (**1**), indicating the presence of the same chromophoric system; its NMR spectrum showed the presence of the new *C*-methyl at δ 2.68, the *N*-methyl being shifted upfield to δ 2.78 from its original value of 2.95 in **1**.

The reduction of **3** to **5** takes place through the intermediary formation of the unstable 7-hydroxymethyldehydronuciferine (**4**), which can be isolated when **3** is reduced under ordinary basic conditions by sodium borohydride. Treatment of alcohol **4** with sodium cyanoborohydride at pH 3 affords 7-methyldehydronuciferine (**5**), presumably via the stabilized iminium ion **6**. Evidence for the ready generation of cation **6** from alcohol **4** was obtained by the interception of cation **6** by hydrogen cyanide to give, in good yield, the crystalline 7-cyanomethyldehydronuciferine (**7**), mp 195–196 °C.

Attempts to effect the direct C-methylation of **1** to **5** by methyl iodide were unsuccessful, presumably because of insufficient nucleophilicity of the C-7 carbon of **1** toward the alkyl halide.

Experimental Section

Melting points are uncorrected. Chromatography was carried out using silica. NMR spectra ($CDCl_3$ containing tetramethylsilane as



internal standard), ultraviolet spectra (ethanol), infrared spectra (KBr), and mass spectra were determined using JEOL-JNH-PS-100 and Perkin-Elmer 202, 137, and 270 spectrometers, respectively. Microanalyses were performed by Midwest Microlab, Indianapolis, Ind.

Dehydronuciferine-7-carboxaldehyde (3). Aqueous sodium hydroxide (2 ml, 50%) was added to a solution of dehydronuciferine[3] (1, 0.360 g) in chloroform (10 ml) containing a few drops of 30% aqueous tetra-*n*-butylammonium hydroxide, and the mixture was stirred for 4 h (external bath at 55–65 °C). After washing with water, the dried organic phase was evaporated and the residue chromatographed (chloroform eluent) to give recovered 1 (0.144 g) and 0.190 g of aldehyde 3, which crystallized from acetone as dark brown prisms: mp 161–163 °C; ir 6.24 μ; uv λ_{max} 213 nm (ϵ 11 000), 261 (24 000), 280 (17 000), 315 sh (7200), 418 (8000); NMR δ 3.30 (s, 3 H, NMe), 3.74 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.03 (t, 2 H, J = 6.5 Hz), 3.52 (t, 2 H, J = 6.5 Hz), 6.88 (s, 1 H, C-3), 10.13 (s, 1 H, CHO), 7.27–9.31 (m, 4 H); mass spectrum *m/e* 321 (M^+, 100), 304 (92), 160.5 (1).

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.76; H, 5.92; N, 4.33. Found: C, 74.86; H, 6.02; N, 4.29.

7-Hydroxymethyldehydronuciferine (4). Excess sodium borohydride was added to a solution of aldehyde 3 (0.050 g) in methanol (10 ml). Examination by TLC after a few minutes showed the absence of any aldehyde. Evaporation, addition of water, and chloroform extraction afforded the alcohol 4 (0.045 g) as a yellow oil which decomposed upon attempted chromatography over silica or alumina. Compound 4 was characterized spectroscopically as follows: uv λ_{max} 260, 325 nm; NMR δ 2.85 (s, 3 H, NMe), 3.21 (t, 2 H, J = 8.5 Hz), 3.28 (t, 2 H, J = 8.5 Hz), 3.86 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 7.08 (s, 1 H, C-3), 7.46–9.76 (m, 4 H); mass spectrum *m/e* 323 (M^+, 100), 308 (55), 306 (55), 292 (25), 290 (20), 161.5 (1).

7-Methyldehydronuciferine (5). A. A solution of alcohol 4 (0.040 g) in tetrahydrofuran (10 ml) was brought to pH 3–4 by the addition of a few drops of 5% hydrochloric acid, and excess sodium cyanoborohydride was added in portions, while maintaining the acidity of the solution. After 15 min, TLC showed no starting material to be present. Workup in the usual manner, followed by crystallization from methanol, gave compound 5 as yellow prisms (0.034 g): mp 99–100 °C; uv λ_{max} 254 nm (ϵ 100 000), 264 (100 000), 324 (25 000), 387 sh (4000); NMR δ 2.68 (s, 3 H, C-Me), 2.78 (s, 3 H, NMe), 3.21 (t, 2 H, J = 8.5 Hz), 3.28 (t, 2 H, J = 8.5 Hz), 3.88 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 7.06 (s, 1 H, C-3), 7.41–9.78 (m, 4 H); mass spectrum *m/e* 307 (M^+, 100), 292 (43), 153.5 (5).

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.17; H, 6.84; N, 4.56. Found: C, 78.00; H, 6.98; N, 4.48.

B. A solution of aldehyde 3 (0.050 g) in methanol (10 ml) was reduced at pH 3–4 with sodium cyanoborohydride as described above for alcohol 4. Workup afforded 5 in 84% yield.

7-Cyanomethyldehydronuciferine (7). Potassium cyanide (0.060 g) was added to a stirred solution of alcohol 4 (0.200 g) in a mixture of ethanol (5 ml) and 1% hydrochloric acid (15 ml). After stirring for 30 min at room temperature, the mixture was heated on the steam bath for 15 min. The usual workup, followed by filtration in chloroform through silica, gave crude nitrile 7. Crystallization from ethanol–chloroform gave 7 as prisms (0.160 g): mp 195–196 °C; ir 4.40 μ; uv λ_{max} 253 nm (sh) (ϵ 35 000), 262 (50 000), 323 (11 000), 370 (2400); NMR δ 2.98 (s, 3 H, NMe), 3.98 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 4.45 (s, 2 H, CH_2CN), 7.13 (s, 1 H, C-3), 7.50–9.75 (m, 4 H); mass spectrum *m/e* 332 (M^+, 100), 317 (57), 292 (49), 166.5 (1).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.90; H, 6.02; N, 8.43. Found: C, 76.03; H. 6.12; N, 8.42.

Acknowledgment. We thank the National Institutes of Health for a grant (CA-11445) in support of this work, and the Fundación Juan March for a supporting fellowship to one of us (J. M. Saá).

Registry No.—1, 7630-74-2; 3, 60538-11-6; 4, 60538-12-7; 5, 60538-13-8; 7, 60538-14-9.

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Gnididione, a New Furanosesquiterpene from *Gnidia latifolia*[1]

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In the course of a continuing search for tumor inhibitors from plant sources, we have isolated the potent antileukemic diterpenoid esters, gnidilatin 20-palmitate and gnidilatidin 20-palmitate, from *Gnidia latifolia* Gilg. (Thymelaeaceae).[2,3] Our isolation procedure also yielded a new sesquiterpene, gnididione (1). Gnididione is the first known guaiane-type sesquiterpenoid with a furan ring.

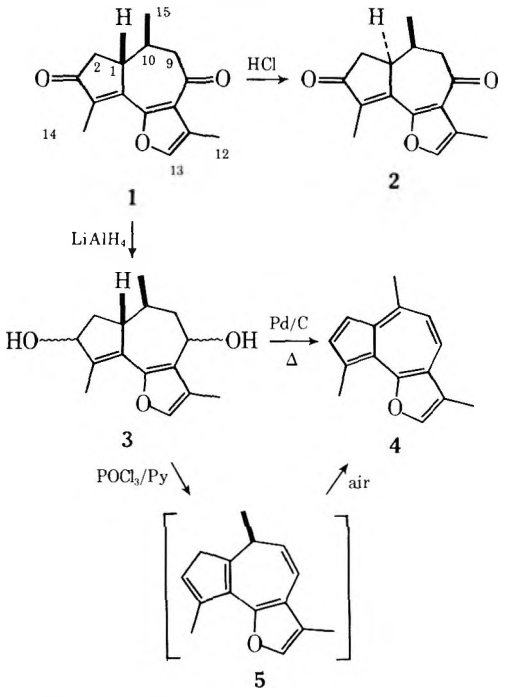
An ethanol extract of *G. latifolia* was partitioned between chloroform and water. The chloroform soluble material was chromatographed on SilicAR CC-7. Crystallization from methanol of the fraction which was eluted with 10% ethyl acetate in benzene gave gnididione (1).

Elemental analysis and mass spectrometry established a molecular formula of $C_{15}H_{16}O_3$ for 1. The ^{13}C NMR spectrum of 1 indicated the presence of two carbonyl groups [δ 206.3 (s) and 195.8 (s)], three double bonds [δ 154.0 (s), 153.6 (s), 142.2 (d), 137.9 (s), 126.5 (s), and 123.4 (s)], two methylene groups [δ 54.1 (t) and 40.7 (t)], two methine groups [δ 46.4 (d) and 32.8 (d)], and three methyl groups [δ 21.8 (q), 10.1 (q), and 9.8 (q)]. Furthermore, the ^1H NMR spectrum showed that one of the methyl groups was attached to a methine group [τ 8.88 (3 H, d, J = 7 Hz)]. The absorptions at 3.22, 6.33, and 6.69 μ in the ir spectrum indicated the presence of a furan ring, and the uv absorption at 338 nm showed that the carbonyl groups, double bond, and furan ring were conjugated. From the above data and from biogenetic considerations, gnididione (1) appeared to belong to the guaiane class of sesquiterpenes and to have either structure 1 or 2. The structure was confirmed by subsequent chemical transformations. Thus, reduction of 1 with lithium aluminum hydride, followed by dehydrogenation over palladium on charcoal, yielded artemazulene (4), which formed a crystalline trinitrobenzene complex. In order to avert possible intramolecular changes during dehydrogenation, the

lithium aluminum hydride reduction product was dehydrated with phosphorus oxychloride in pyridine to give intermediate **5**, which was very unstable and was autoxidized by air to give artemazulene (**4**).

Isomerization of gnididione (**1**) with hydrochloric acid in ethanol yielded isognididione (**2**). In view of the mild conditions employed for the conversion of gnididione (**1**) to isognididione (**2**), epimerization at the C-1 position seemed likely. The uv and ir spectra of **2** were virtually identical with those of **1**, indicating little change in the chromophore during isomerization. Moreover, the $[\alpha]_D$ values of **1** and **2** were +370 and −313°, respectively, a difference which is compatible with isomerization at C-1 (Chart I, **1** → **2**).

Chart I

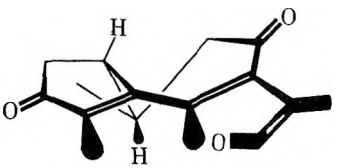


The configuration of the C-15 methyl group relative to the C-1 proton was determined by a comparison of the ^1H NMR spectra of **1** and **2**. In **1** the methyl resonance (3 H, d, J = 7 Hz, 15-H) was at τ 8.88, whereas in **2** the methyl resonance was shifted to τ 9.20 as a result of its close proximity to the 6,7 double bond (Figure 1). Thus, H-1 and C-15 are cis in gnididione (**1**) and trans in isognididione (**2**). The absolute configuration of gnididione has not yet been established.

Experimental Section

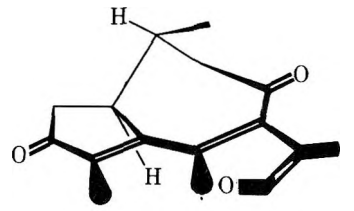
General. Melting points were determined on a Mettler Model FP2 hot stage and are uncorrected. Ultraviolet and visible absorption spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on Perkin-Elmer Model 257 and Model 337 recording spectrophotometers. Nuclear magnetic resonance spectra were determined on either a Varian HA-100 spectrometer or a JEOL PS-100 pulsed FT NMR spectrometer interfaced to a Texas Instrument JEOL 980A computer, with tetramethylsilane as an internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalysis was carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. All thin layer chromatography utilized silica gel 60 precoated glass plates (E. Merck), and visualization of TLC was effected with short wavelength uv and concentrated sulfuric acid–vanillin–ethanol (20:1:3) spray.

Isolation of Gnididione (1) from *Gnidia latifolia*. The dried ground stem wood and stem bark (30 kg) of *Gnidia latifolia* was extracted at room temperature by stirring with 95% ethanol (216 l.) for 24 h. The extraction mixture was filtered and concentrated below 30 °C in vacuo, to a syrupy residue (~900 ml). The residue was partitioned between chloroform (3 × 8 l.) and water (10 l.). The combined chloroform layers were concentrated to give a brown tar (440 g), which was chromatographed on a SilicAR CC-7 (Mallinkrodt) column (5 kg) by eluting with benzene followed by benzene containing increasing amounts of ethyl acetate. Elution with 10% ethyl acetate in benzene gave a fraction (65 g) which gave plates upon crystallization from methanol. Recrystallization from methanol gave gnididione (**1**, 20 g, 0.067%): mp 110–111 °C; $[\alpha]^{29}_D$ +372° (c 0.97, $CHCl_3$); uv max (EtOH) λ (ϵ) 238 (7170), 259 (7650), 338 nm (19 700); ir (KBr) 3.22, 3.41, 5.95, 6.10, 6.22, 6.33, 6.69, 12.58 μ; NMR ($CDCl_3$) τ 8.88 (3 H, d, J = 7 Hz, 15-CH_3), 7.98 (3 H, d, J = 2 Hz, 14-CH_3), 7.85 (3 H, d, J = 1 Hz, 12-CH_3), 7.70–7.00 (6 H, m, 1-, 2-, 9-, and 10-H), 2.65 (1 H, q, J = 1 Hz, 13-H); mass spectrum m/e 244 (M^+), 216, 201, 187, 174, 117, 91, 77.



$[\alpha]_D$ +372°

1



$[\alpha]_D$ −313°

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Figure 1.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.73; H, 6.75.

Artemazulene (4). Method A. A solution of gnididione (**1**, 1 g) in THF (5 ml) was added to a suspension of lithium aluminum hydride (0.5 g). The mixture was stirred at room temperature for 1 h. Excess reagent was decomposed with saturated sodium potassium tartrate solution, the precipitate was removed, and the filtrate was concentrated at reduced pressure to give a white powder (1.1 g). This was mixed with 10% palladium on charcoal (1 g) and heated at about 300 °C for 10 min. The reaction mixture was extracted with hexane (50 ml) to give a dark blue oil (150 mg), which was chromatographed on alumina (Woelm; neutral, activity II, III) to give artemazulene (**4**, 15 mg). The theoretical amount of 1,3,5-trinitrobenzene was added and the complex, crystallized twice from methanol, was identified as the artemazulene derivative by melting point (188–189 °C, lit.[4] mp 187–188 °C) and uv, visible, and ir spectra.

Method B. Phosphorus oxychloride (1.5 ml) was added to a solution of the lithium aluminum hydride reduction product (1.1 g) in pyridine at 0 °C under nitrogen. After 2 h the reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was evaporated and chromatographed on alumina (Woelm; 20 g, neutral, activity II, III) to give **5** (430 mg): NMR ($CDCl_3$) τ 8.77 (3 H, d, J = 7 Hz, 15-CH_3), 8.04 (3 H, d, J = 1.5 Hz, 14-CH_3), 7.86 (3 H, br s, 12-CH_3), 7.42 (1 H, d of q, J = 6, 7 Hz, 10-H), 7.07 (2 H, br s, 2-H), 4.93 (1 H, d of d, J = 6, 10 Hz, 9-H), 4.20 (1 H, q, J = 1.5 Hz, 3-H), 3.80 (1 H, d, J = 10 Hz, 8-H), 2.96 (1 H, br s, 13-H). Intermediate **5** was rapidly oxidized by air to give artemazulene (**4**, 380 mg).

Isognididione (2). Hydrochloric acid (2 N, 2 ml) was added to a solution of gnididione (100 mg) in ethanol (3 ml). The mixture was heated at reflux temperature for 18 h, then extracted with chloroform. The chloroform layer was evaporated and separated on silica gel plates to give gnididione (48 mg) and isognididione, as a homogeneous, amorphous solid (**2**, 36 mg): $[\alpha]^{24}_D$ −313° (c 1.365, $CHCl_3$); uv (EtOH) λ (ϵ) 237 (8200), 258 (8800), 336 nm (20 000); ir (KBr) 3.21, 3.42, 5.92, 6.05, 6.23, 6.32, 6.67, 12.50 μ; NMR ($CDCl_3$) τ 9.20 (3 H, d, J = 7 Hz, 15-CH_3), 7.97 (3 H, d, J = 2 Hz, 14-CH_3), 7.86 (3 H, br s, 12-CH_3), ca. 7.9 (1 H, 10-H), 7.29, 7.85 (each 1 H, m, 2-H), 7.01, 7.24 (each 1 H, m, 9-H), 6.68 (1 H, br m, 1-H), 2.73 (1 H, br s, 13-H); mass spectrum m/e 244.1106 (M^+, calcd for $C_{15}H_{16}O_3$, 244.1099).

Registry No.—**1**, 60498-89-7; **2**, 60498-90-0; **4**, 478-51-3; **5**, 60498-91-1.

References and Notes

(1) This investigation was supported by research grants from the National Cancer Institute (CA-11718 and CA-12059) and the American Cancer Society (CI-102K), and contracts with the Division of Cancer Treatment, NCI, National Institutes of Health (N01-CM-12099 and N01-CM-67002).
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Synthesis of Antibacterial *p*-Quinols from Marine Sponges. Synthetic Applications of "Masked" Quinones

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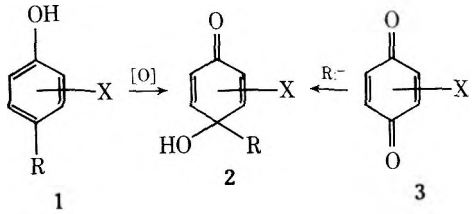
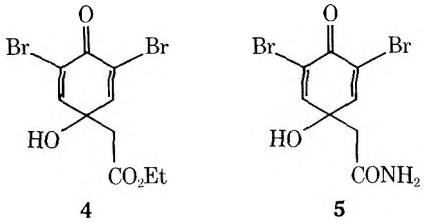
o- and *p*-quinols, including closely related derivatives, are important intermediates in the biosynthesis and metabolism of phenolic natural products.[2] Recently, research in this laboratory[3] and elsewhere[4] has been directed toward exploiting such versatile intermediates in the synthesis of naturally occurring quinones and alkaloids.

In principle, there are two potentially attractive routes to the synthesis of *p*-quinols such as **2**, one being the oxidation of the appropriately substituted phenol **1**, and the other being the regioselective nucleophilic addition of a carbon nucleophile ($R:^-$) to the quinone moiety **3**. Historically, the use of



1 2 3

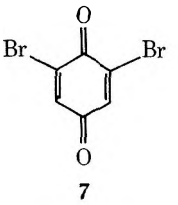
phenol oxidation techniques as an effective means of producing *p*-quinols has been quite disappointing;[5] however, with the recent development of selective oxidants such as thallium(III),[6] these phenol oxidations may now be considered as viable synthetic processes. Recently, we have developed the capability of regioselectively monoprotecting substituted *p*-quinones **3**, and have demonstrated that such substrates are excellent general precursors to *p*-quinols.[7] The purpose of this note is to report on the application of such methodology to the synthesis of *p*-quinol antibiotic metabolites **4** and **5**



4 5

recently isolated from the mollusk *Tylodina fungina*, and marine sponges of the genus *Verongia*, respectively.[8]

The requisite monoprotected *p*-quinone **8** was readily prepared in two steps from commercially available precursors. 2,4,6-Tribromophenol (**6**) was oxidized with thallium tris(trifluoroacetate), according to the method of Taylor,[9] to 2,6-dibromo-*p*-benzoquinone (**7**) in 67% yield.[10] Regiospecific carbonyl protection of the requisite quinone carbonyl was realized upon treatment of **7** with 1 equiv of trimethylsilyl cyanide (TMSCN) and a catalytic amount of triphenylphosphine in acetonitrile at 0 °C. *Under these conditions the adduct* **8** *was produced in essentially quantitative yield uncontaminated by the isomeric quinone adduct* **9**. A change



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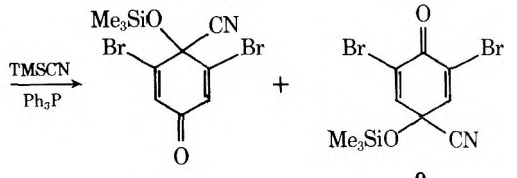

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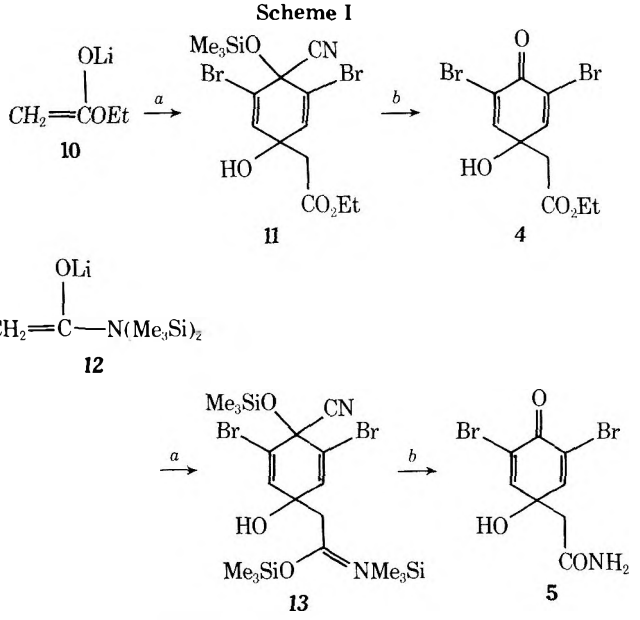
in solvent (C_6H_6, CCl_4, $CHCl_3$) or increased reaction temperatures resulted in a loss in regioselectivity of the reaction. For example, the same reaction carried out in chloroform (25 °C, 1 h) afforded an **8**:**9** ratio of 38:62. Tentative conclusions relating to the relative stabilities of the isomeric adducts were obtained from an equilibrium experiment. Treatment of **8** with a catalytic amount of triphenylphosphine at 40 °C (240 h) in acetonitrile resulted in an apparent isomerization to **9** ($K_{eq} \geq 10$).

With the requisite "masked" quinone **8** in hand, the *p*-quinol ester **4** and amide **5** were readily prepared via the enolate carbonyl addition processes outlined in Scheme I. A tetrahydrofuran solution of lithioethyl acetate (**10**) was gen-

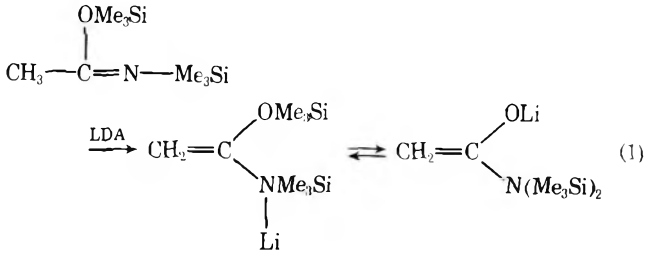
Scheme I



a, **8**, −100 °C, NH_4Cl-H_2O; b, AgF, H_2O-THF.

erated according to established procedures,[11] and then cooled to −100 °C, whereupon a tetrahydrofuran solution of blocked quinone **8** was added over a period of a few seconds. The reaction mixture was allowed to warm to 0 °C over a 2-h period, and quenched with 1 equiv of ammonium chloride. The resultant dark crude blocked quinol **11** was immediately deblocked with 1 equiv of silver fluoride in THF–water (10:1).[3] The flocculent mixture was stirred at room temperature for 2.5 h to yield the desired quinol **4**[8b] in a 77% overall yield from masked quinone **8**.

Owing to the general acid and base lability of *p*-quinols,[12] a simple acetamide enolate equivalent was desired for the construction of quinol acetamide **5**. Toward this end the lithiation of *N,O*-bis(trimethylsilyl)acetamide (BSA)[13] with lithium diisopropylamide (LDA) was investigated (eq 1). Treatment of BSA with 1 equiv of LDA (−78 °C) under



standard conditions[11] afforded the enolate **12** which can presumably exist as either of the two tautomeric species shown above. Addition of the masked quinone **8** to enolate **12** under conditions identical with those followed by ester enolate **10** afforded the adduct **13**. Quinone deprotection with aqueous silver fluoride with concomitant hydrolysis of the amide-protecting silyl ligands afforded the quinol acetamide **5** in 37% overall yield. The physical and spectroscopic data reported for both **4** and **5** are identical with those obtained for the compounds prepared via this route.[8b,14]

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Beckman infrared spectrophotometer Model 4210. Nuclear magnetic resonance spectra were taken on a Varian Associates A-60D spectrometer. The mass spectra were recorded on a Du Pont MS 21-492B double focusing mass instrument at an ionizing voltage of 70–75 eV. Ultraviolet spectra were recorded on a Cary 14 instrument.

The term "dry tetrahydrofuran" refers to purification of the commercial material by distillation from lithium aluminum hydride under anhydrous conditions. "Dry acetonitrile" and "dry diisopropylamine" were obtained by distillation of the solvent from calcium hydride. TMSCN and BSA were purchased from Silar Laboratories Inc.

3,5-Dibromo-4-cyano-4-trimethylsilyloxy-2,5-cyclohexadienone (8). A 25-ml flask equipped with magnetic stirring bar and drying tube was charged with 102 mg (0.38 mmol) of 2,6-dibromo-*p*-benzoquinone (**7**) in 5 ml of dry acetonitrile, and the solution cooled to 0 °C. To the cold, stirred, yellow solution was added 0.05 ml of TMSCN (distilled from CaH_2) and 3 mg of triphenylphosphine. Stirring was allowed to continue at 0 °C for 1 h.

The solvent was removed in vacuo to yield 144 mg (100%) of a crude oil. Molecular distillation yielded a clear yellow oil: bp 110 °C (bath temperature) (0.022 mm); ir ($CHCl_3$) 3000 (methyls), 1665 cm^{-1}; NMR ($CDCl_3$) δ 0.35 (s, 9 H, $-Me_3Si$), 6.75 (s, 2 H, vinyl CH). The undistilled adduct **8** is quite pure and may be utilized without further purification.

Anal. Calcd for $C_{10}H_{11}Br_2NO_2Si$: C, 32.89; H, 3.04; Br, 43.77; N, 3.84; O, 8.76; Si, 7.69. Found: C, 32.98; H, 3.02.

General Procedure for the Preparation of Lithium Diisopropylamide. A solution of dry diisopropylamine in dry tetrahydrofuran was placed under nitrogen and cooled to between −50 and −20 °C (dry ice–2-propanol). To the clear, colorless solution was added 1 equiv of *n*-butyllithium (Alfa Inorganics) maintaining the temperature in the above range. The mixture was allowed to stir for an additional 5-min, and finally cooled to −78 °C (dry ice–2-propanol).

General Procedure for the Synthesis of Masked Quinols. To a cooled (−78 °C) solution of lithium diisopropylamide (1 equiv) in tetrahydrofuran was added 1 equiv of ethyl acetate or BSA. After stirring at −78 °C for 30 min, the enolate solution was then cooled to −100 °C (ether–liquid nitrogen). A solution of blocked quinone **8** in dry tetrahydrofuran was then added, and the reaction allowed to warm to 0 °C over a 2-h period, and quenched with 1 equiv of ammonium chloride in a minimum volume of water. The reaction was finally transferred onto sodium sulfate with dichloromethane. After filtration through Celite–sodium sulfate, the solvent was removed in vacuo to yield the crude masked quinol.

2,6-Dibromo-4-carboethoxymethyl-4-hydroxy-2,5-cyclohexadienone (4). A solution of lithium diisopropylamide (1.41 mmol) was prepared from 0.20 ml (1.41 mmol) of dry diisopropylamine and 0.58 ml (1.41 mmol) of *n*-butyllithium (2.44 M, hexane) in 10 ml of dry tetrahydrofuran. Reaction of 513 mg (1.41 mmol) of 2,6-dibromo blocked quinone **8** with 0.14 ml (1.41 mmol) of ethyl acetate under the above conditions yielded 602 mg of the corresponding masked quinol **11** as a crude, dark brown oil: NMR ($CDCl_3$) δ 0.30 (s, 9 H, Me_3SiO-), 1.43 (t, J = 7 Hz, 3 H, $-CO_2CH_2CH_3$), 2.69, 2.80 (s, 2 H, epimeric $-CH_2CO_2Et$), 4.20, 4.22 (q, J = 7 Hz, 2 H, epimeric $-CO_2CH_2CH_3$), 6.77 (s, 2 H, vinyl CH).

Deblocking of 602 mg (1.33 mmol) of **11** with 169 mg (1.33 mmol) of silver fluoride in 10 ml of THF–H_2O (10:1) was accomplished by stirring at room temperature for 2.5 h. The reaction mixture was diluted with dichloromethane and filtered, and the filtrate was washed successively with water and brine and dried (Na_2SO_4). The solvent was removed in vacuo to yield 400 mg of a clear, crude, dark brown oil established as 90% pure by gas chromatography (77% yield based on masked quinone **8**). Preparative thin layer chromatography on silica gel (ether eluent) gave a light tan solid, which was sublimed, and finally recrystallized twice from hexane–dichloromethane to yield analytically pure white needles: sublimed at 70 °C (bath temperature) (0.017 mm); mp 127.0–127.5 °C (lit. 121 °C);[8b] ir ($CHCl_3$) 3570 (free OH), 3470 (H-bonded OH), 3030, 2980, 1705 (ester C=O), 1685 cm^{-1} (dienone C=O); NMR ($CDCl_3$) δ 1.29 (t, J = 7 Hz, 3 H, $-CO_2CH_2CH_3$), 2.76 (s, 2 H, $-CH_2CO_2Et$), 4.18 (s, 1 H, *OH*), 4.25 (q, J = 7 Hz, 2 H, $-CO_2CH_2CH_3$), 7.41 (s, 2 H, vinyl CH); uv (CH_3OH) λ_{max} 257 nm (ε 9596); *m/e* 351.895 ± 0.003 (calcd for $C_{10}H_{10}Br_2O_4$, 351.895).

Anal. Calcd for $C_{10}H_{10}Br_2O_4$: C, 33.93; H, 2.85; Br, 45.15; O, 18.08. Found: C, 33.68; H, 2.82.

2,6-Dibromo-4-(carbamoylmethyl)-4-hydroxy-2,5-cyclohexadienone (5). A solution of lithium diisopropylamide was prepared from 0.52 ml (3.71 mmol) of dry diisopropylamine and 1.52 ml (3.71 mmol) of *n*-butyllithium (2.44 M, hexane) in 25 ml of dry tetrahydrofuran. Reaction of 1.35 g (3.71 mmol) of masked quinone **8** with 755 mg (3.71 mmol) of BSA under the above conditions yielded 1.53 g of the corresponding masked quinol **13** as a dark green foam: NMR ($CDCl_3$) δ 2.52 (s, 2 H, CH_2), 6.47 (s, 2 H, vinyl CH). Without purification **13** was treated with 338 mg (2.66 mmol) of silver fluoride in 16 ml of THF–H_2O (15:1) at room temperature for 6 h. Isolation of quinol acetamide **5** according to the procedure described for **4** afforded 1.06 g a dark foam which was purified by preparative thick layer chromatography on silica gel (ethyl acetate eluent). The resultant light tan solid, 441 mg, mp 188–190 °C (37%), was recrystallized three times from acetone–ether to give analytically pure colorless needles: mp 194–195 °C (lit. 195–196 °C);[8b] NMR (acetone-d_6) δ 2.79 (s, 2 H, CH_2), 7.59 (s, 2 H, vinyl C-H); uv (CH_3OH) λ_{max} 257 nm (ε 8315); *m/e* 322.881 ± 0.003 (calcd for $C_8H_7Br_2NO_3$, 322.879).

Anal. Calcd for $C_8H_7Br_2NO_3$: C, 29.57; H, 2.17; Br, 49.18; N, 4.31; O, 14.77. Found: C, 29.71; H, 2.30.

Acknowledgment. This work has been supported by the National Institutes of Health, Grant CA-17904.

Registry No.—**4**, 24744-57-8; **5**, 17194-81-9; **7**, 19643-45-9; **8**, 60498-69-3; **11**, 60498-70-6; **13**, 60498-71-7; TMSCN, 7677-24-9; lithium diisopropylamine, 4111-54-0.

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Secalonic Acids D and F Are Toxic Metabolites of *Aspergillus aculeatus*

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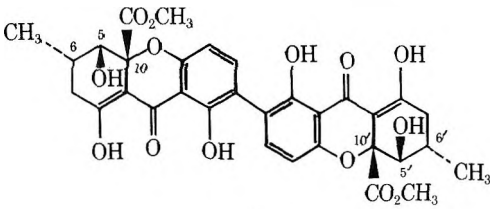
Continuing our studies of toxic substances produced by food spoilage fungi, we have investigated the metabolites of *Aspergillus aculeatus* Iizuka grown on white corn. Purification of the crude methylene chloride extracts by petroleum ether precipitation and subsequent preparative thin layer chromatography on silica gel yielded two toxic metabolites, secalonic acid D and F. Secalonic acid D has previously been isolated from *Penicillium oxalicum*.[3] Other secalonic acids are known metabolites of *Aspergillus ochraceus* (secalonic acid A),[4] *Claviceps purpurea* (secalonic acids, A, B, C)[5] and *Phoma terrestris* (secalonic acids, A, E).[6] Secalonic acid F is a new member of this group. In the following, we report the chemical identification, preparation and biological activity of the two toxins of *A. aculeatus* Iizuka. The more polar compound, obtained as yellow needles, was identical with secalonic acid A[7] as judged by comparison of infrared, ultraviolet, mass, and proton magnetic resonance spectra. Its optical rotation, $[\alpha]^{20}D$ +64° (*c* 0.14, $CHCl_3$), however, was opposite in sign from that of secalonic acid A and hence the toxin



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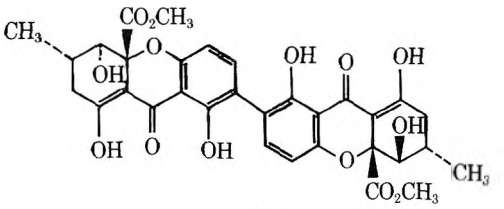

2

is secalonic acid D (**1**)[3] (ergochrome EE), the enantiomer of secalonic acid A.

The second toxin crystallized from benzene–cyclohexane in the form of yellow needles, $[\alpha]^{20}D$ +190° (*c* 0.131, pyridine), *m/e* 638.15987 (calcd for $C_{32}H_{30}O_{14}$, 638.16356).[8] It was soluble in aqueous potassium carbonate, gave a positive ferric chloride test, and exhibited ultraviolet and infrared absorptions typical for secalonic acids.[5,9] The aromatic region of the proton magnetic resonance spectrum displayed four one-proton doublets at δ 6.51, 6.55, 7.30, and 7.33 each with a coupling constant of 8 Hz indicating that the new substance was an unsymmetrical dimer.[10] This hypothesis received further support from the appearance of the carbinol proton signals at C-5 and C-5′. A broad singlet at δ 4.08 and a doublet at δ 3.88, J = 11 Hz, suggest that hydroxyl and methyl groups are cis and trans oriented, respectively, in the two structural moieties. The circular dichroism spectrum was found to exhibit a large positive Cotton effect at 333 nm and comparison with values obtained for other secalonic acids[11] left no doubt that both C-10 and C-10′ have the *R* configuration. If it is assumed, in analogy to all known secalonic acids and ergochromes, that the C-6 and C-6′ methyl groups are trans to the C-10 and C-10′ carbomethoxy groups, respectively,[11–13] the new toxin, which we have named secalonic acid F (ergochrome BE),[14] should have structure **2**. This was confirmed as follows. When submitted to oxidation with potassium permanganate secalonic acid F (**2**) gave (*S*)-(−)-methylsuccinic acid[11] identical with a sample obtained by analogous oxidation of secalonic acid D (**1**). The two metabolites showed antimicrobial activity against *Bacillus megaterium*,[15] secalonic acid F being somewhat less active than secalonic acid D. Secalonic acid A had been reported to inhibit *Bacillus subtilis* and *Piricularia oryzae* but not other tested microorganisms.[4] Toxicity data will be presented in a forthcoming paper by Professor Gerald N. Wogan, Department of Nutrition and Food Science, M.I.T.

Experimental Section

Melting points were measured on a Kofler hot stage or a Büchi SMP20 oil bath apparatus and are corrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. The following spectrometers were used: IR, Perkin-Elmer 567; ultraviolet, Cary 14; ^1H NMR, Hitachi Perkin-Elmer R22 90 MHz; CD, Cary 60; mass spectra, Hitachi Perkin-Elmer RMU-6L and CEC 110B (Du Pont Industries).

Aspergillus aculeatus Iizuka was screened on a variety of grains in 2.8-l. Fernbach flasks on the shaker for 10 days at 30 °C.[15] The best were white corn and minute rice. The more traditional procedure of unagitated fermentation on glutinous rice yielded no toxin. After growth on white corn, the cultures were homogenized in a blender with methylene chloride, the homogenate was filtered, and the methylene chloride filtrate was concentrated in vacuo. Precipitation with petroleum ether gave ~400 mg of toxic petroleum ether insolubles (PEI)/kg of substrate corn. The PEI (814 mg) was dissolved in 40 ml of hot methylene chloride and filtered to remove 50 mg of nontoxic precipitate. The filtrate was concentrated in vacuo and chromatographed on silica gel GF254 plates containing 6% tartatic acid (solvent 2-pentanone–chloroform, 2:8). Two yellow bands (R_f 0.17 and 0.29), which both gave red-brown ferric chloride tests, contained toxic substances.

Secalonic Acid D (1). The slow-moving band (R_f 0.17) yielded 94 mg of a yellow glass which was crystallized first from carbon tetrachloride and then from chloroform to give 74 mg (9.1% of PEI) of light yellow needles (mp 281–283 °C in evacuated capillary, 255–259 °C on hot stage). High-resolution mass spectrum M^+ 638.16088 (calcd for $C_{32}H_{30}O_{14}$, 638.16353); $[\alpha]^{25}D$ +64° (*c* 0.14, chloroform); UV max (ethanol) 236, 265, and 338 nm (ε 17 800, 15 100, and 37 800); ^1H NMR (Me_2SO-d_6–1% Me_4Si) δ 1.05 (d, 6 H, J = 4 Hz), 2.0–3.0 (m, 6 H), 3.63 (s, 6 H), 3.80 (d of d, 2 H, J = 6 and 10 Hz), 6.02 (d, 2 H, J = 6 Hz, exchanges), 6.64 (d, 2 H, J = 8 Hz), 7.47 (d, 2 H, J = 8 Hz), 11.70 (s, 2 H, exchanges), 13.72 (bs, 2 H, exchanges); CD (*c* 2.9 × 10^{-2} mg/ml dioxane) λ 400 (Δε 0), 332 (+13.5), 290 (0), 270 (−4), 260 (−1.5), 225 (−48), 215 (−23). Further, the compound was found to have TLC behavior (silica gel GF254 containing 6% tartaric acid, solvent 2-pentanone–chloroform, 2:8) and an IR spectrum [(KBr) 3505, 1735, 1610, 1585, 1432, 1232, and 1061 cm^{-1}] identical with those of an authentic sample of secalonic acid A.

Oxidation of Secalonic Acid D (1). Secalonic acid D (54 mg) was dissolved in 5 ml of 2 N sodium hydroxide. The solution was cooled to 0 °C and added to 5 ml of saturated potassium permanganate solution at 0 °C. The reaction mixture was maintained at 0 °C for 48 h and then clarified at 0 °C with sulfur dioxide. Extraction with ethyl acetate (3 × 50 ml) gave 40 mg of crude reaction products which were chromatographed on a 1-mm Avicel F plate (solvent ammonia–1-propanol, 3:7, developed twice). The desired band (R_f 0.37) was eluted

from the cellulose with 40 ml of methanol–water (9:1). Removal of the methanol in vacuo followed by partitioning of the aqueous residue between 1 N hydrochloric acid (10 ml) and ethyl acetate (2 × 25 ml) gave 2.6 mg of crystalline, ethyl acetate soluble residue. Crystallization (benzene–cyclohexane) gave 1.9 mg of (*S*)-(−)-methylsuccinic acid, mp 109–110 °C, $[\alpha]^{25}D$ −12° (c 0.09, ethanol). IR ($CHCl_3$) and mass spectra were identical with spectra of authentic, racemic methylsuccinic acid.

Secalonic Acid F (2). The fast-moving band (R_f 0.29) yielded 53 mg of a yellow glass which upon crystallization (benzene–cyclohexane) gave 26 mg (3.2% of PEI) of yellow needles, mp 218–221 °C (hot stage), 253–256 °C (evacuated capillary). A high-resolution mass spectrum indicated M^+ 638.15987 (calcd for $C_{32}H_{30}O_{14}$, 638.16356). Secalonic acid F showed $[\alpha]^{20}D$ +202°, $[\alpha]^{20}_{578}$ +214° (c 0.13, pyridine); UV max (ethanol) 236, 263, and 388 nm (ε 19 250, 17 300, 37 000); IR (KBr) 3520, 1748, 1610, 1590, 1442, 1238, 1068, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 6 H, *J* = 7 Hz), 2.0–3.0 (m, 6 H), 2.67 (b, 1 H, exchanges), 2.86 (b, 1 H, exchanges), 3.67 (s, 6 H), 3.87 (d, 1 H, *J* = 10 Hz), 4.09 (b, 1 H), 6.52 (d, 1 H, *J* = 9 Hz), 6.58 (d, 1 H, *J* = 9 Hz), 7.35 (d, 1 H, *J* = 9 Hz), 7.39 (d, 1 H, *J* = 9 Hz), 11.65 (s, 1 H, exchanges), 11.80 (s, 1 H, exchanges), 13.70 (s, 1 H, exchanges), 13.88 (s, 1 H, exchanges); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 638 (20), 579 (100), 561 (20), and 501 (20); CD (*c* 4.8 × 10^{-2} mg/ml dioxane) λ 400 nm (Δε 0), 332 (+17), 275–260 (0), 223 (−43), and 215 (−25).

Oxidation of Secalonic Acid F (2). Secalonic acid F (57 mg) was oxidized with potassium permangate as described for secalonic acid D to give 2.6 mg of (*S*)-(−)-methylsuccinic acid, mp 109–111 °C, $[\alpha]^{25}D$ −13° (*c* 0.12, ethanol). IR ($CDCl_3$) and mass spectra were identical with spectra of authentic racemic methylsuccinic acid.

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Registry No.—**1**, 35287-69-5; **2**, 60687-07-2; (*S*)-(−)-methylsuccinic acid, 2174-58-5.

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A Synthesis of (±)-Methyl *n*-Tetradeca-*trans*-2,4,5-trienoate, an Allenic Ester Produced by the Male Dried Bean Beetle *Acanthoscelides obtectus* (Say)[1]

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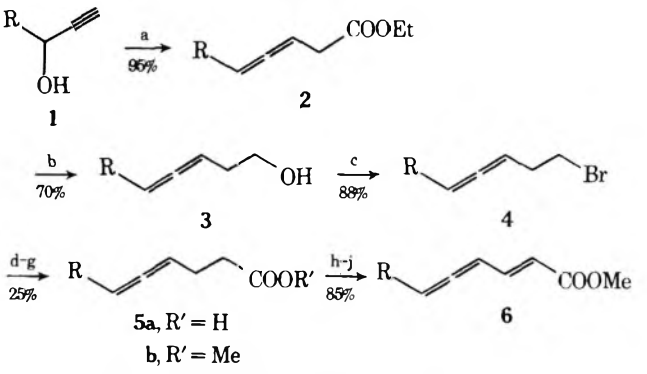
In 1970, Horler[2] isolated a novel optically active allenic ester from the hexane extracts of male dried bean beetles [*Acanthoscelides obtectus* (Say)] for which structure **6** was suggested based on spectrometric and chemical evidence. Subsequent total synthesis has corroborated the assigned structure.[3-6] As a putative sex pheromone, there are two aspects of **6** which are unusual: first, the compound is present in rather large amounts (ca. 0.5% of the body weight) compared with other insect sex pheromones, and second, the ester **6** is unstable ($t_{1/2}$ = 10 h at room temperature) and polymerizes readily. We report below a synthesis of racemic **6** starting with undec-1-yn-3-ol (**1**).

The synthetic plan outlined in Scheme I (R = *n*-octyl) was conceived with two strategic strictures in mind: (1) an intermediate (e.g., carboxylic acid **5a**) was desired which could be resolved and later used to ascertain the absolute configuration

Scheme I



a, $CH_3C(OEt)_3$, EtCOOH, 135 °C; b, $(i\text{-Bu})_2AlH/C_6H_6$–hexane, 0 °C; c, CBr_4–Ph_3P/CH_2Cl_2, 0 °C; d, Mg/THF; e, CO_2; f, H_3O^+; g, MeOH, *p*-TsOH; h, $(i\text{-Pr})_2NLi$/THF, −78 °C; i, PhSeSePh; j, $NaIO_4$/THF–H_2O, 25 °C, 10 h

(as yet unknown) of the allenic moiety, and (2) the instability inherent in the conjugated allenenic ester suggested that the introduction of the completely conjugated chromophore be relegated to the last step of the synthesis. A key intermediate **5** which fulfills these requirements was prepared in essentially four steps from the acetylenic alcohol **1**[7] (Scheme I).

A modified Claisen rearrangement[8,9] converted **1** to the β-allenic ester **2** in 95% yield. Reduction of **2** to the corresponding alcohol **3** with lithium aluminum hydride gave poor yields of **3**; rather, the predominant reaction was proton abstraction from the highly activated position α to the ester function (as evideced by copious gas evolution) whereupon subsequent aqueous workup returned an isomeric mixture of methyl trideca-2,4-dienoates as the major product.[10] The desired reduction was successfully achieved in 70% yield with diisobutylaluminum hydride.

The reaction of the homoallenic alcohol **3** with PBr_3 under a variety of conditions gave poor yields of the desired substitution product **4**.[11] However, the bromide **4** was conveniently prepared in 76% yield from the alcohol **3** using CBr_4–Ph_3P in CH_2Cl_2 at ice bath temperatures. Although the analogous chlorination with CCl_4–PPh_3 has been amply documented,[12] the corresponding bromination has received only sporadic attention[13] despite the often preferable reaction properties of the bromides. Since we could find no systematic evaluation of the scope and limitation of this mild bromination, we have examined a number of additional cases. Invariably, primary alcohols gave good yields of the bromide (see Table I). With the exception of 2-octanol, which gave a 90% yield of 2-bromooctane, secondary alcohols such as 3-pentanol and cyclohexanol gave consistently poor yields of the bromide. Thus the synthetic utility of the reaction appears to be restricted to primary bromides, in which case we found that best yields were obtained when the reactions were run in CH_2Cl_2 at 0–25 °C in the presence of 1.25 equiv of CBr_4 and 1.5 equiv of Ph_3P.

Table I

Alcohol	Registry no.	% yield of bromide	Registry no.
Geraniol	106-24-1	82	6138-90-5
(*Z*)-Non-3-en-1-ol	10340-23-5	89	60705-54-6
Undeca-3,4-dien-1-ol	13994-61-1	88	60705-55-7
Oleyl alcohol	143-28-2	92	6110-53-8
1-Octanol	111-87-5	91	111-83-1
2-Octanol	123-96-6	90	557-37-5

Introduction of the final carbon of the chain was effected by carboxylation of the Grignard reagent derived from **4**[14] to give the crude acid **5a** in ~30% yield, which was not purified but converted directly to the methyl ester **5b.** The major product of the reaction, hexacosa-9,10,16,17-tetraene, was derived from coupling of the homoallenic bromide. This marked propensity for coupling was not alleviated by using a large excess of magnesium and slow addition. Nonetheless, the ease of separation of the acid permitted the preparation of ester **5b** in 25% overall yield from **4.**

The thermal instability of the final allenenic ester required that the last step of the sequence, the introduction of unsaturation between C-2 and C-3 of the ester **5b,** be conducted under the mildest possible conditions. The efficiency and trans stereoselectivity of the selenoxide elimination of Sharpless and co-workers[15] seemed ideally suited to the case at hand. Thus, the lithium enolate of **5b** reacted with diphenyl diselenide to give the α-phenylseleno ester which was oxidized to the corresponding selenoxide with $NaIO_4$ in aqueous THF to give, after 10 h at room temperature, the desired allenenic ester **6** in 85% yield. The spectral properties of synthetic **6** were identical with those reported for the natural product.[2]

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer, NMR spectra with a Varian HA-100 instrument using Me_4Si as an internal standard, and mass spectra with a Du Pont 29-491B spectrometer. Extracts were dried over $MgSO_4$. Unless otherwise stated, Bakerflex chromatographic sheets were used for analytical TLC separations using phosphomolybdic acid as developer.

Ethyl Trideca-3,4-dienoate (2). The experimental procedure of Henrick and co-workers[9] was used. From 19.0 g (113 mmol) of undec-1-yn-3-ol (**1**),[7] 128 g (792 mmol, 7 equiv) of $CH_3C(OEt)_3$, and 400 mg of propionic acid was obtained 25.7 g (95%) of **2** as a colorless oil: bp 98–100 °C (0.15 mm); IR (CCl_4) 1961, 1740 cm^{-1}; NMR (CCl_4) δ 5.0–5.2 (m, 2 H) 4.1 (q, 2 H), 2.9 (dd, 2 H), 2.2–2.6 (m, 2 H), 1.2–1.8 (m, 12 H), 1.25 (partially hidden t, 3 H), 0.9 (distorted t, 3 H); MS (70 eV) *m/e* 238 (M^+, 20%), 57 (100%).

Trideca-3,4-dien-1-ol (3). To a magnetically stirred solution of 11.9 g (15.1 ml, 84 mmol) of diisobutylaluminum hydride in 70 ml of 3:1 benzene–hexane was added a solution of 10.0 g (42 mmol) of ester **2** in 15 ml of benzene at a rate sufficient to maintain the temperature at ≤5 °C. After addition was complete, the mixture was allowed to stir under nitrogen for an additional 45 min at 0 °C. After excess diisobutylaluminum hydride was destroyed by dropwise addition of *i*-PrOH, the clear, colorless solution was transferred to a separatory funnel and added dropwise to 55 ml of 3 M H_2SO_4 with ice bath cooling and rapid magnetic stirring. The organic layer was washed with 2 × 50 ml of saturated $NaHCO_3$, 2 × 25 ml of H_2O, and 25 ml of brine. After drying, the solvent was removed in vacuo and the residue short path distilled to give 5.75 g (70%) of the alcohol **3** as a colorless oil: bp 82–83 °C (0.1 mm); IR (CCl_4) 3610, 1960 cm^{-1}; NMR (CCl_4) δ 5.0 (m, 2 H), 4.2 (br s, 1 H), 3.5 (t, 2 H), 2.0 (m, 4 H), 1.6–1.1 (br, 12 H), 0.9 (distorted t, 3 H); MS (70 eV) *m/e* 196 (M^+, 3%), 98 (100%).

1-Bromotrideca-3,4-diene (4). To a magnetically stirred solution of 1.96 g (10.0 mmol) of the alcohol **3** and 4.15 g (12.5 mmol) of CBr_4 in 15 ml of CH_2Cl_2 was added portionwise with ice-bath cooling 3.92 g (15.0 mmol) of Ph_3P. After addition was complete, the mixture was stirred for an additional 5 min, whereupon the solvent was removed in vacuo. Ether (15 ml) was added and the mixture filtered. The filter cake was washed with 3 × 10 ml of ether. The combined filtrate and washings were concentrated in vacuo and the residue distilled via Kugelrohr to give 2.28 g (88%) of the bromide as a nearly colorless oil: bp 70 °C (bath) (0.3 mm); IR (CCl_4) 1960 cm^{-1}; NMR (CCl_4) δ 5.15 (m, 2 H), 3.4 (t, 2 H), 2.5 (m, 2 H), 1.95 (m, 2 H), 1.3 (br, 12 H), 0.9 (distorted t, 3 H).

The alcohols listed in Table I were brominated on a 10-mmol scale as described above.

Methyl Tetradeca-4,5-dienoate (5b). A flame-dried 100-ml three-neck flask fitted with a magnetic stirrer, condenser, addition funnel, and nitrogen inlet was charged with 5.15 g (212 mg-atoms, 10 equiv) of Mg and 20 ml of THF freshly distilled from Na. A crystal of iodine was added and after several minutes 3 drops of the bromide **3** was introduced. When the iodine color discharged, the remainder of 4.89 g (21.2 mmol) of the bromide in 5 ml of THF was added dropwise over the course of 1 h with rapid magnetic stirring. After addition was complete, the mixture was allowed to stir at ambient temperature for 4 h, whereupon CO_2 gas (dried by passage through concentrated H_2SO_4 followed by anhydrous $CaSO_4$) was introduced for 30 min. The reaction mixture was poured into dilute, iced H_2SO_4 and the products extracted into ether. A TLC of the ether layer using ether–hexane (1:1) as eluent showed two major spots corresponding to the acid **5a** (R_f 0.2) and the coupling product (R_f 0.6). The carboxylic acid was extracted into 2 × 10 ml of 1.5 M NaOH and recovered by acidification with 3 M H_2SO_4 followed by extraction into ether. The ether layer was washed with water, dried, and concentrated in vacuo to a pale yellow oil which proved to be one major component (R_f 0.2) by TLC.

The crude acid was dissolved in 10 ml of MeOH to which was added 1 ml of $CH_3C(OMe)_3$ and 10 mg of *p*-TsOH. After standing at room temperature for 24 h, the mixture was concentrated in vacuo to ~⅓ volume, diluted with ether, and washed with saturated $NaHCO_3$. After drying and concentrating in vacuo, the residue was distilled via Kugelrohr to give 1.10 g (25%) of the ester **5b** as a colorless oil: bp 90 °C (bath) (0.3 mm); IR (CCl_4) 1960, 1740 cm^{-1}; NMR (CCl_4) δ 5.0 (m, 2 H), 3.6 (s, 3 H), 2.3 (m, 4 H), 1.9 (m, 2 H), 1.3 (br, 12 H), 0.9 (distorted t, 3 H); MS (70 eV) *m/e* 238 ($M^{\cdot+}$, 10%), 140 (100%).

The major, nonacidic coupling product was isolated in 50–60% yield and purified by Kugelrohr distillation: bp 120 °C (bath) (0.3 mm); IR (CCl_4) 1960 cm^{-1}; NMR (CCl_4) δ 5.0 (m, 4 H), 2.0 (m, 8 H), 1.4 (m, 34 H), 0.9 (distorted t, 6 H); MS (70 eV) *m/e* 368 (M^+).

Methyl Tetradeca-*trans*-2,4,5-trienoate (6). A flame-dried 25-ml three-neck flask fitted with a condenser, addition funnel, magnetic stirrer, and rubber septum was charged with 2.5 ml (4.0 mmol) of 1.6 M *n*-BuLi/hexane and 5 ml of THF freshly distilled from Na. Diisopropylamine (0.41 g, 4.0 mmol) was added via syringe and the mixture cooled to −78 °C. With rapid magnetic stirring, 0.47 g (2.0 mmol) of the ester **5b** in 5 ml of THF was added dropwise. The mixture was stirred under nitrogen at −78 °C for an additional 0.5 h whereupon 0.625 g (2.0 mmol) of diphenyl diselenide in 3 ml of THF was added dropwise. After a further 1 h of stirring at −78 °C, the cooling bath was removed and 10 ml of saturated NH_4Cl added. The product was extracted into 25 ml of ether and the organic layer washed with 2 × 15 ml of 10% Na_2CO_3 and dried. Evaporation of the solvent in vacuo gave a dark yellow residue which was chromatographed on silica gel packed in hexane. Unreacted diphenyl diselenide (75 mg) was eluted with hexane. The α-phenylseleno ester was then eluted with 10% Et_2O in hexane.

The α-phenylseleno ester was dissolved in 8 ml of THF. A solution of 1.08 g (5.0 mmol) of $NaIO_4$ in 4 ml of warm water was added in one portion and the mixture allowed to stir at ambient temperature for 10 h. Analytical TLC (10% ether in hexane) showed a single major component. The reaction mixture was diluted with ether, washed with 2 × 15 ml of 10% Na_2CO_3, dried, and concentrated in vacuo to give 0.39 g (85%) of the allenenic ester **6** as a pale yellow oil:[16] IR (CCl_4) 1940, 1720, 1630, and 980 cm^{-1}; NMR (CCl_4) δ 7.1 (dd, 1 H, J = 15, 10 Hz), 5.75 (d, 1 H, J = 15 Hz), 5.7, 5.3 (m, 2 H), 3.6 (s, 3 H), 2.1 (m, 2 H), 1.3 (br, 12 H), 8.9 (distorted t, 3 H); MS (70 eV) *m/e* 236 ($M^{\cdot+}$, 25%), 138 (95%), 79 (100%).

Acknowledgments. We would like to thank the SUNY Research Foundation and the Research Corporation for financial support. We are further indebted to Mr. Jon Stickles and Dr. Bruce Norcross for technical assistance.

Registry No.—**1,** 60705-48-8; **2,** 60705-49-9; **3,** 60705-50-2; **4,** 60705-51-3; **5a,** 60705-52-4; **5b,** 60705-53-5; **6,** 34656-68-3; $CH_3C(OEt)_3$, 78-39-7; CBr_4, 558-13-4; $CH_3C(OMe)_3$, 1445-45-0; hexacosa-9,10,16,7-tetraene, 60705-56-8; diphenyl diselenide, 1666-13-3; methyl α-phenylselenotetradeca-*trans*-2,4,5-trienoate, 60705-57-9.

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(16) The crude allenenic ester 6 was a single major component by TLC. Rapid chromatography on silica gel packed in CH_2Cl_2 was used to remove selenium-containing contaminents with little loss in material. The thermal instability of 6 precluded purification by vapor phase chromatography.

Stereospecific Synthesis of (2*S*,3*R*)-2-Amino-3-mercaptobutyric Acid—an Intermediate for Incorporation into β-Methyllanthionine-Containing Peptides

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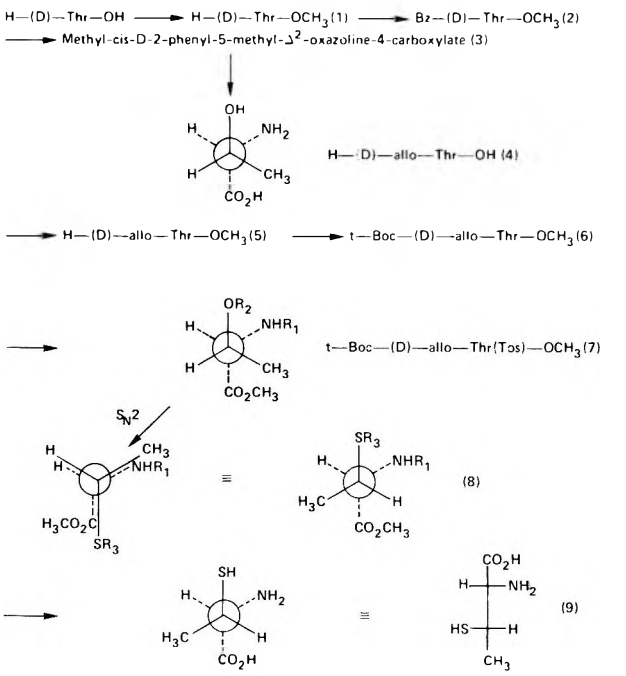
Access to the correct isomer[1] of β-methyllanthionine is a prerequisite for the synthesis of fragments of heterodetic polycyclic peptides, such as nisin.[2] A reasonable approach requires the preparation of *threo*-β-methyl-D-cysteine. Formation of the thioether bridge is anticipated to be accomplished by a substitution or addition reaction on a suitable alanine derivative before or after incorporation into the peptide chain.

Carter et al.[3] prepared the diastereoisomeric pairs of *S*-benzyl-β-methylcysteine which they called amino acids A and B and which have been assigned the threo and allo configurations, respectively.[1]

Hoogmartens et al.[4] began with the same method of preparation and by derivatization and crystallization with the aid of optically active bases resolved each of the pairs into the respective D and L amino acid.

This procedure is elaborate if only one of the four possible isomers is desired. Yields of the final product are low as the result of lack of stereospecificity in the synthesis.

We have devised a stereospecific synthesis outlined in the scheme (R_1 = *tert*-butyloxycarbonyl; R_2 = tosyl; R_3 = acetyl) below. Good yields of the desired isomer are obtained by a series of simple steps in a relatively short time. The crucial step involves an SN2 displacement of tosylate by thiolacetate anion. Although the products of such reactions are often mixtures resulting from elimination, O-alkylation of thiolacetate, or SN1 mechanisms, no evidence for these processes was observed here. Examination of the crude reaction mixture after hydrolysis and S-benzylation showed the only sulfur



containing product to be *threo*-*S*-benzyl-β-methyl-D-cysteine. A small amount of unreacted *allo*-*O*-tosyl-D-threonine was also present but had no effect on the subsequent steps.

The reactions were also applied to *allo*-DL-threonine and gave pure *allo*-β-methyl-DL-cysteine as determined by S-benzylation and amino acid analysis.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the National Institutes of Health. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter.

Amino acid analyses were performed on a modified Phoenix analyzer using the Moore, Stein, and Spackman system. *S*-Benzyl-β-methylcysteines were analyzed on a 60 × 0.9 cm column using pH 4.25, 0.2 N Na citrate buffer at a flow rate of 60 ml/h. Elution volumes of the threo and allo isomers of *S*-benzyl-β-methylcysteine are 163 and 187 ml, respectively.

Countercurrent distribution was run in a 200 tube Craig machine with lower and upper phase volumes of 10 ml each.

D-Threonine Methyl Ester Hydrochloride (1). D-Threonine, 180 g, $[\alpha]^{23}D$ +30.5° (*c* 1, water) [lit.[7] $[\alpha]^{26}D$ +28° (*c* 1–2, water)], obtained from Pierce, Rockford, Ill., was refluxed twice for 1 h in 1.5 l. of 2 N HCl in methanol to give 205 g (98%) of **1** as an oil which crystallized on standing under vacuum.

***N*-Benzoyl-D-threonine Methyl Ester (2).** **1** (205 g) was benzoylated without further purification by the dropwise addition of 175 ml of benzoyl chloride (1.5 mol) to a solution in 1.5 l. of water–dioxane (2:1) over 1 h using 5 N NaOH to maintain a pH of 8.5–9.0 and an ice bath to keep the temperature at 30 °C. The dioxane was removed under reduced pressure and the aqueous phase extracted with ethyl acetate. Evaporation of the solvent yielded 285 g (80%) of crude **2**. Recrystallization from benzene gave 220 g (63%) of pure **2**, mp 92–94 °C, $[\alpha]^{22}D$ −22.0° (*c* 8, ethanol) [lit.[5] mp 96.0 °C, $[\alpha]^{26}D$ −23.2° (*c* 6, ethanol)].

Methyl *cis*-D-2-Phenyl-5-methyl-Δ²-oxazoline-4-carboxylate (3). **3** (205 g, 0.875 mol) was prepared by treating **2** with thionyl chloride (twice distilled from triphenyl phosphite[6]) according to the literature.[5]

***allo*-D-Threonine (4).** Crude crystalline **3** (205 g) was hydrolyzed in 1 l. of 6 N HCl at 90 °C for 5 h. Workup according to the literature[5] yielded 76 g (65% based on **2**) of pure **4**, $[\alpha]^{27}D$ −32.5° (*c* 8, 1 N HCl in water) [lit.[5] *allo*-L-threonine $[\alpha]^{27}D$ +32.5° (*c* 8.2, 1 N HCl in water)].

***allo*-D-Threonine Methyl Ester Hydrochloride (5).** **4** (75 g, 0.625 mol) was esterified in the same manner as D-threonine. The yield

was 103 g (97%) of crude crystalline material from which 1 g was recrystallized from methanol–ether to give 0.9 g of pure product. $[\alpha]^{23}D$ −23.1° (c 5, methanol), mp 115 °C. Anal. Calcd for $C_5H_{12}NO_3Cl$: C, 35.41; H, 7.13; N, 8.26; Cl, 20.91. Found: C, 35.33; H, 7.39; N, 8.45; Cl, 20.70.

***allo*-Boc-D-threonine Methyl Ester (6).** Crude **5** (103 g, 0.61 mol) was dissolved in 1 l. of dry (Linde 4A) dimethyl sulfoxide and 170 ml (1.22 mol) of triethylamine was added with vigorous stirring. After the addition of 90 ml (0.67 mol) of *tert*-butyloxycarbonyl azide the mixture was stirred for 48 h at room temperature. The volume was reduced to 200 ml under vacuum before 1 l. of ice water was added. Following acidification to pH 2.5 with citric acid the solution was extracted with five 200-ml portions of ethyl acetate. The combined extracts were washed with $NaHCO_3$ solution. Evaporation of the solvent after drying over Na_2SO_4 gave 124 g (87%) of a pale yellow oil, $[\alpha]^{23}D$ +14.4° (c 5.0, ethanol). Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 50.80; H, 8.53; N, 5.80.

***allo*-Boc-*O*-tosyl-D-threonine Methyl Ester (7).** **6** (124 g, 0.53 mol) was dissolved in 400 ml of pyridine (distilled and stored over 4A sieves) and cooled to 0 °C. Tosyl chloride (133 g, 0.70 mol, recrystallized from petroleum ether) was added in portions over 10 min to maintain a temperature of 0–5 °C. The solution stood at 5 °C for 30 h and was then poured onto 1 l. of crushed ice and stirred for 0.5 h. The oily precipitate was extracted into 1.5 l. of ether and washed with ice-cold 0.01 N HCl (5–6 l.) to an acid reaction and finally with water to neutrality. Evaporation of the ether after drying over Na_2SO_4 yielded 189 g (91%) of crude **7**. Although the racemic compound crystallized readily, **7** resisted and was purified by extraction into cyclohexane–petroleum ether (1:1) at 37 °C and precipitation in the cold. Final yield of purified product 147 g (71%); homogeneous by TLC and showing the same R_f as the crystalline racemate; $[\alpha]^{19}D$ +4.2° (c 8, ethanol). Anal. Calcd for $C_{17}H_{25}NO_7S$: C, 52.70; H, 6.50; N, 3.62; S, 8.28. Found: C, 53.48; H, 6.58; N, 3.53; S, 9.33.[8]

***threo*-Boc-*S*-acetyl-β-methyl-D-cysteine Methyl Ester (8).** **7** (90.8 g, 0.227 mol) was dissolved in 300 ml of DMF (purified by passage over a column of acidic Al_2O_3 Brockman activity I and stored over 4A sieves). The solution was divided equally among five 100-ml Kjeldahl flasks.

Potassium thiolacetate was prepared by the addition of a 10% excess of thiolacetic acid to a methanolic solution of KOH. The solvent was removed on a rotary evaporator and excess thiolacetic acid under high vacuum. A water solution of the salt had a pH of 5.5.

After cooling to 0 °C, the Kjeldahl flasks were cleared of oxygen by alternate application of vacuum and nitrogen; 7.8 g (0.07 mol) of potassium thiolacetate was added, and each flask was again flushed, and prior to sealing under vacuum equipped with a magnetic stirring bar. The reaction was allowed to proceed with stirring at room temperature for 36 h although a copious precipitate of potassium tosylate appeared within 0.5 h. The contents of the reaction vessels were combined and the DMF removed in vacuo. The residue was extracted with 250 ml of ethyl acetate and washed with three 150-ml portions of water. Upon evaporation of the ethyl acetate 53 g (75%) of an orange oil was obtained, $[\alpha]^{23}D$ −55.6° (c 5, ethanol). Examination of an analytical amount by amino acid analysis after hydrolysis and oxidation with performic acid revealed the presence of 90% of the expected amount of β-methylcysteic acid and 10% of threonine. The product was considered pure enough for the subsequent steps in the synthesis. For the purpose of characterization 3 g was subjected to 1250 transfers in a countercurrent distribution machine [solvent system chloroform–benzene–methanol–water (1:1:1.5:0.5)] to yield 2.2 g of a pale yellow oil, K = 0.105, 99% pure by amino acid analysis, $[\alpha]^{23}D$ −66.1° (c 5, ethanol). Anal. Calcd for $C_{12}H_{21}NO_5S$: C, 49.47; H, 7.26; N, 4.80; S, 11.01. Found: C, 49.38; H, 7.57; N, 4.74; S, 12.63.[8] **7** (100 mg), K = 0.092, was also isolated. A fraction comprising the intersection of the incompletely resolved thiol ester and tosylate accounted for another 500 mg. Amino acid analysis showed this fraction to be 70% thiol ester.

***threo*-2-Amino-3-mercapto-D-butyric Acid (9).** Crude **8** (50 g, 0.172 mol) was exposed for 0.5 h to 100 ml of trifluoroacetic acid at room temperature. The acid was evaporated in vacuo and the product dissolved in 150 ml of 12 N HCl and heated to 65 °C for 5 h. Evaporation of the solution gave a yellow oil which solidified on lyophilization. The material was dissolved in 900 ml of ethanol and treated with 1 equiv of NH_4OH. Upon cooling 12.4 g of a white, crystalline product was obtained. A further 2 g remained in the mother liquor, overall yield 65%. The product (300 mg) was allowed to react with benzyl bromide in liquid ammonia to give in 80% yield (2*S*,3*R*)-2-amino-3-benzylthiolbutyric acid on precipitation from neutral aqueous solution and crystallization from ethanol. The compound was pure by amino acid analysis, $[\alpha]^{22}D$ −76.2° (c 1, 1 N HCl) [lit.[3] $[\alpha]^{25}D$ −72.0° (c 1, 1 N HCl)]. The disulfide desired for the preparation of derivatives was obtained by air oxidation of 7.0 g of **9** over a period of 4 days in 200 ml of aqueous ammonia at pH 8.6. After recrystallization from water–ethanol 5.6 g (80%) of a white hemihydrate was obtained. The product was homogeneous by amino acid analysis, $[\alpha]^{19}D$ −414° (c 1, 1 N HCl). Anal. Calcd for $C_8H_{17}N_2O_{5.5}S_2$: C, 34.77; H, 6.20; N, 10.14; S, 23.20. Found: C, 34.69; H, 6.10; N, 10.06; S, 22.64.[8]

Registry No.—**1**, 60538-15-0; **2**, 60538-16-1; **3**, 60538-17-2; **4**, 24830-94-2; **5**, 60538-18-3; **6**, 60538-19-4; **7**, 60538-20-7; **8**, 60538-21-8; **9**, 43083-49-4, D-threonine, 632-20-2; benzoyl chloride, 98-88-4; thionyl chloride, 7719-09-7; *tert*-butyloxycarbonyl azide, 1070-19-5; tosyl chloride, 98-59-9; potassium thiolacetate, 10387-40-3; β-methylcysteic acid, 60538-22-9; (2*S*,3*S*)-2-amino-3-benzylthiolbutyric acid, 60538-23-0.

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Prostaglandins and Congeners.[1] 11. Synthesis of *dl*-13-Hydroxyprostanoic Acids

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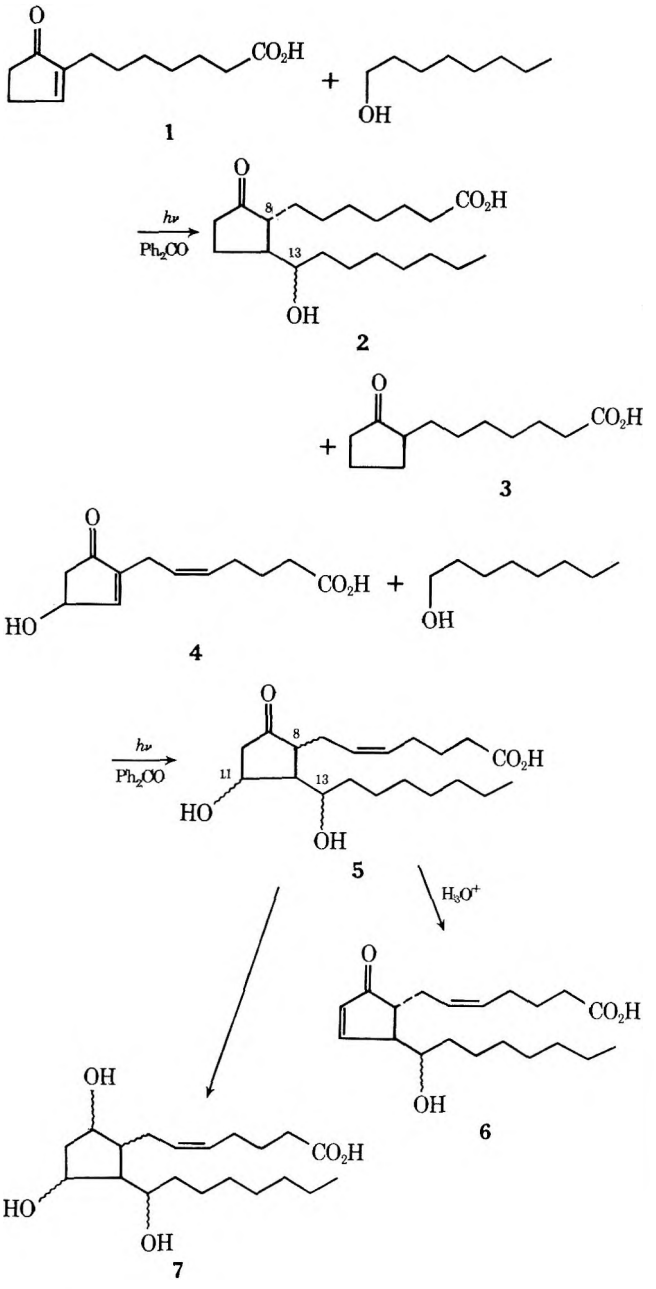
In an effort to prepare biologically more selective prostaglandin congeners, a program was initiated in our laboratory involving the synthesis of congeners in which the 15-hydroxy function was shifted to other positions in the β chain. In a previous report we have described the synthesis and biological properties of prostaglandin analogues wherein the 15-hydroxy group is moved to the C_{16}, C_{17}, and C_{20} position or is replaced by a hydroxymethyl group.[2] Another group has reported compounds wherein the hydroxy group is placed at C_{14}.[3] We now describe a convenient synthesis of prostaglandin congeners wherein the hydroxy function has been shifted to the C_{13} position. After this work was completed, two reports appeared concerning the synthesis of 13-hydroxyprostanoic acids which do not contain the 11-hydroxy substituent.[4] Our synthesis, which is different, is also applicable to the synthesis of 13-hydroxyprostaglandins which contain this biologically important 11-hydroxy group.

dl-9-Oxo-13-hydroxyprostanoic acid (**2**) is conveniently obtained by the benzophenone sensitized photoaddition of 1-octanol to the cyclopentenone **1**[5] using a 350-nm light source and a Pyrex reaction vessel.[6] Since 1-octanol also serves as the solvent, the product is isolated by sodium hydroxide extraction, which also serves to epimerize any 8-iso isomers to the corresponding 8-normal isomers, followed by silica gel chromatography. 13-Hydroxyprostaglandin **2** is obtained as two C_{13} epimers, separable by thin layer chromatography. The major side product of this reaction has been identified as the conjugate reduction product **3**.

In a similar manner photoaddition of 1-octanol to 4-hydroxycyclopentenone **4**[7] gives, after extraction with sodium bicarbonate solution and silica gel chromatography, *dl*-9-

oxo-11,13-dihydroxyprosta-(5*Z*)-enoic acid (**5**) as a mixture of isomers. Silica gel chromatography has allowed a partial



separation of isomers. That both 8-iso and 8-normal isomers were isolated is evidenced by epimerization experiments. However, the configuration at C_{11} is uncertain; it is likely that both the 11α and 11β isomers are formed.

On treatment with dilute hydrochloric acid in THF, **5** is converted to *dl*-9-oxo-13-hydroxyprosta-(5*Z*),10-dienoic acid (**6**). The course of this reaction was monitored by TLC; it was apparent that epimerization of the 8-iso isomers to the corresponding 8-normal isomers was competitive with PGA formation under these conditions; consequently the trans configuration for **6** can be assigned.

Reduction of **5** with lithium perhydro-9b-boraphenalylhydride gives *dl*-9,11,13-trihydroxyprosta-(5*Z*)-enoic acid (**7**).

Experimental Section

***dl*-9-Oxo-13-hydroxyprostanoic Acid (2).** A mixture of 18.4 g (0.0875 mol) of 2-(6-carboxyhexyl)cyclopent-2-en-1-one (**1**)[5] and 3.75 g of benzophenone was dissolved in 260 ml of 1-octanol. The solution was placed in a Pyrex tube and was flushed with nitrogen. The solution was then irradiated in a Rayonet reactor (Model MGR-100) using a 3500-Å light source for 4 days. The solution was then mixed with 150 ml of hexane and a solution of 8.0 g of NaOH in 300 ml of water. The mixture was stirred for 20 min. The aqueous layer was separated and the organic layer was washed with 100 ml of water. The combined aqueous solutions were then washed three times with ether. The aqueous solution was then acidified with HCl. The mixture was extracted with ether. The ether solution was washed with a saturated solution of NaCl and then dried over $MgSO_4$. The solvent was removed and the residue (26.5 g) was chromatographed on a dry column of silica gel eluting with benzene–ethyl acetate (2:1) containing 0.5% acetic acid to give a fraction containing 11.2 g (0.033 mol) of **2** as a mixture of two isomers: NMR δ_{Me_4Si} ($CDCl_3$) 6.73 (bs, 2 H, OH), 3.70 (m, 1 H, CHOH), 2.31 (t, 2 H, CH_2CO_2H), 2.45–1.10 (m's, 28 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3455 (OH), 1730 cm^{-1} (C=O); MS *m/e*, 340 (M^+), 322 ($M - H_2O$).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.42; H, 10.60.

The two isomers can be separated by thin layer chromatography on silica gel using a solvent mixture consisting of ethyl acetate–benzene (2:3), 1% acetic acid.

From a less polar fraction was obtained 1.7 g of the conjugate reduction product **3** identified by comparison with an authentic sample.[5]

***dl*-9-Oxo-11,13-dihydroxyprosta-(5*Z*)-enoic Acid (5).** A solution of 5.4 g (0.024 mol) of **4**[7] and 1.47 g of benzophenone in 100 ml of 1-octanol was placed in a Pyrex tube and irradiated (3500 Å) under nitrogen for 43 h. The solution was poured into a cold solution of 9.0 g of $NaHCO_3$ in 130 ml of water. To this was added 130 ml of hexane. The organic layer was separated and discarded. The aqueous layer was washed three times with ether and then acidified (HCl) at 0 °C. The mixture was extracted with ether. The ether solution was washed with water and saturated NaCl. The ether solution was dried ($MgSO_4$). The ether was removed to give 5.8 g of a yellow oil. This was chromatographed on a 5 ft × 3 in. dry column of silica gel eluting with ether containing 0.5% acetic acid. Fractions 18–31 contained 2.01 g of a lower R_f isomer mixture; fractions 35–37 contained 0.5 g of a higher R_f isomer(s). For the lower R_f isomer mixture: NMR δ_{Me_4Si} ($CDCl_3$) 6.00 (bs, 3 H, OH), 5.43 (m, 2 H, vinyl), 4.47 and 4.10–3.56 (m's, 2 H, CHOH), 3.00–1.10 (m's, 24 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3370 (OH), 1720 cm^{-1} (C=O); high-resolution MS, 336.2309 [calcd for $C_{20}H_{34}O_5$ ($M - H_2O$), 336.2300]. For the higher R_f isomer(s): NMR δ_{Me_4Si} ($CDCl_3$) 5.65 (bs, 3 H, OH), 5.45 (m, 2 H, vinyl), 4.64 (m, 1 H, CHOH), 3.87 (m, 1 H, CHOH), 2.92–1.00 (m's, 24 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3370 (OH), 1722cm^{-1} (C=O); high-resolution MS, 336.2306 [calcd for $C_{20}H_{34}O_5$ ($M - H_2O$), 336.2300].

That the higher R_f fraction is composed of one or more 8-iso isomers is evidenced by that fact that on treatment with dilute HCl in THF or brief treatment with K_2CO_3 in methanol–water, it is epimerized to a material with the same R_f as the more polar isomer mixture.

***dl*-9-Oxo-13-hydroxyprosta-(5*Z*),10-dienoic Acid (6).** A solution of 0.4 g (1.12 mmol) of **5** as a mixture of isomers in 15 ml of THF containing 8 ml of 1.5 N HCl was allowed to stand at room temperature under a nitrogen atmosphere for 2 days. The mixture was poured into water and extracted with ether. The ether solution was washed with a saturated solution of NaCl and dried over $MgSO_4$. The solvent was removed and the residue was chromatographed on three 200-mμ silica gel plates developing with ethyl acetate–benzene (1:1) containing 2% acetic acid. From the major band was isolated 0.325 g of **6** as a mixture of two C_{13} isomers: NMR δ_{Me_4Si} ($CDCl_3$) 7.72 and 7.60 (dd's, 1 H, vinyl β to C=O in each isomer, J = 2.2, 6.0 Hz), 7.67 (bs, 2 H, OH's), 6.24 (m, 1 H, vinyl α to carbonyl), 5.42 (m, 2 H, vinyl), 3.72 (m, 1 H, CHOH), 2.77 (m, 1 H, ring allylic proton), 2.55–1.90 (m's, 7 H, allylic, α to C=O), 1.90–1.10 (m, 16 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3330, 1707, 1585 cm^{-1}; UV (CH_3OH) 223 nm (ϵ 8100).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.00; H, 9.36.

***dl*-9,11,13-Trihydroxyprosta-(5*Z*)-enoic Acid (7).** To a solution of 0.5 g (1.41 mol) of **5** as a mixture of isomers in 20 ml of THF was added at −20 °C under nitrogen with stirring 7.3 ml of 0.5 M THF solution of lithium perhydro-9b-boraphenalylhydride (3.67 mmol). The solution was allowed to warm up to 5 °C over a 1-h period. To the solution was added a solution of 0.3 g of NaOH in 5 ml of water followed by 2 ml of 30% H_2O_2. After brief stirring, the mixture was poured into water. The water layer was washed with ether and then acidified with HCl. The mixture was extracted with ether. The ether solution was dried over $MgSO_4$. The ether was removed leaving 0.52 g of **7** as a mixture of isomers: NMR δ_{Me_4Si} ($CDCl_3$) 5.55 (m, 6 H, vinyl and OH's), 4.00–4.10 (m, 2 H, ring CHOH's), 3.94–3.50 (m, 1 H, chain CHOH), 2.55–1.10 (m's, 24 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR

(neat) 3340, 1710 cm^{-1}; MS *m/e* 338 ($M - H_2O$), 320 ($M - 2H_2O$).

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.64; H, 9.94.

Acknowledgment. I wish to thank Mr. L. Brancone and his staff for microanalyses, and Messrs. W. Fulmor and G. Morton and Dr. R. T. Hargreaves and staff for spectral data. I would also like to thank Dr. M. J. Weiss for many helpful discussions.

Registry No.—1, 5239-43-0; (13*R*)-2, 60676-39-3; (13*S*)-2, 60676-40-6; 4, 54556-60-4; (8α)-5, 60733-21-3; (8β)-5, 60676-41-7; (13*R*)-6, 60676-42-8; (13*S*)-6, 60676-43-9; 7, 60676-44-0; 1-octanol, 111-87-5.

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Influence of a 9α-Fluorine on the Epoxidation of an 11β-Hydroxy-Δ^4-3-keto Steroid with Basic Hydrogen Peroxide

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Epoxidation of Δ^4-3-keto steroids with hydrogen peroxide and base generally gives the β 4,5-epoxide as the major or exclusive product.[1] Various polar substituents including the 11β-hydroxyl group increase the proportion of α epoxide produced. We describe herein the effect of a 9α-fluorine on the epoxidation of an 11β-hydroxy steroid.

Reaction of enone **1a** with hydrogen peroxide and sodium hydroxide in methanol was complete in 4 h. From the resulting mixture of epoxides (ca. 2:1 ratio based on the intensity of the C-19 methyl signals in the NMR spectrum) the major isomer was isolated and characterized as the β epoxide **2a** by consideration of the molecular rotation difference (+4°) that attends the conversion of **1a** to **2a** (comparison values[2] for the cholestane and pregnan-20-one series are found in Table I).

Epoxidation of **1b** under identical conditions proved to be both slower and more stereoselective. After 4 days a 49% yield of a single epoxide and 25% of unreacted **1b** were obtained. The molecular rotation difference (−19.8°) suggested that this epoxide was the β isomer **2b**. Because of the uncertain influence of the 1,3-diaxial interaction (F–C-4) in **2b** on conformation and optical rotation, we decided to provide further evidence for the stereochemistry of **2b**.

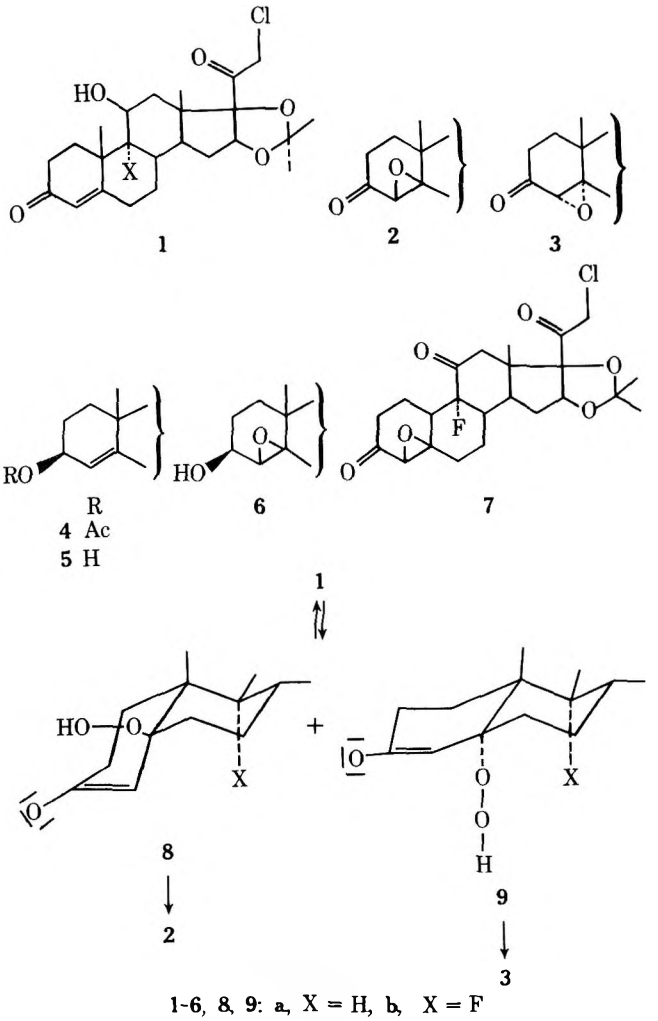
Epoxidation of allylic alcohols with peracid, which occurs on the side cis to the hydroxyl group,[3] provides the basis for the preparation of epoxy ketones of known stereochemistry provided that the requisite allylic alcohol is available.[4] Reduction of **1b** with sodium borohydride gave a single allylic alcohol **5b** after purification via its acetate **4b**. β stereochemistry is assigned to **5b** based on comparison of the molecular rotation differences in Table I with those for **4b** (−298.5°) and **5b** (−230°).[5] The NMR spectrum of **5b** is also consistent with this conclusion as the vinylic hydrogen lacks the characteristic (6–10 Hz) coupling expected for the α epimer which contains a pseudoequatorial 3β hydrogen.[6]

Table I. Molecular Rotation Differences

	Δ[M]D cholestane[a]	Δ[M]D pregnan-20-one[a]
4α,5α-Epoxid-3-one	−510.8	−546.1
4β,5β-Epoxid-3-one	+174	+108
3β-OH-Δ^4-Ene	−152.9	−199.6
3β-OAc-Δ^4-Ene	−299.9	−291.4
3α-OH-Δ^4-Ene	+106.1	
3α-OAc-Δ^4-Ene	+418.1	

[a] Based on conversion of the Δ^4-3-one to the functionality indicated. Values of optical rotation from ref 2 were used to calculate these molecular rotation differences.

Epoxidation of **5b** with *m*-chloroperbenzoic acid followed by Jones oxidation of the crude product gave a single epoxy triketone (**7b**) via epoxy alcohol **6b** in 70% yield. Oxidation of



2b with Jones reagent gave the same epoxide **7b**. This sequence establishes the stereochemistry of **2b** as β and validates the use of molecular rotation differences in spite of the diaxial interaction present in **2b**.

The effect of the 9α-fluorine in **1b** on both the rate and stereochemistry of epoxidation is attributable to the steric and field effects present in transition states leading from intermediates 8 and 9 to epoxides **2** and **3**, respectively. Henbest[1] has suggested that (when X = H) more strain is released in the transition state leading from **8a** to **2a** than in that from **9a** to

3a. The presence of a larger fluorine atom in **8b** and **9b** should increase this difference. Similarly, relief of the electrostatic repulsion between the pseudoaxial enolate anion at C-4 and the axial fluorine atom in **8b** should be more important than relief of the corresponding interaction in **9b**. Both steric and electrostatic effects therefore favor the formation of the observed β-epoxide **2a**.

Experimental Section

Optical rotations were determined in chloroform at ambient temperature on a Perkin-Elmer 141 polarimeter. NMR spectra were determined in deuteriochloroform on Varian A-60 or XL-100 spectrometers. Preparative thin layer chromatography was performed with Merck silica gel plates (PF-254, 20 × 20 × 0.2 cm).

21-Chloro-4β,5-epoxy-11β-hydroxy-2',2'-dimethyl-5β-pregnano[16α,17-*d*][1,3]dioxolane-3,20-dione (2a). A solution of 3 g (0.00662 mol) of **1a** ([α]D +153°, *c* 0.56) in 300 ml of methanol was stirred with 7.2 ml (0.07 mol) of 30% hydrogen peroxide and 4.8 ml (0.0192 mol) of 4 N sodium hydroxide solution. After 4 h no **1a** could be detected by TLC and the solution was diluted with water and extracted with chloroform to give 2.0 g of a mixture of epoxides **2a** and **3a** in the ratio of ca. 2:1. Preparative TLC using chloroform–ethyl acetate (3:1) as the developing solvent gave a pure sample of the major isomer **2a** (higher R_f material), mp 265–267 °C from methanol, [α]D +154° (*c* 0.45). A similar sample had mp 262–264 °C and [α]D +145.5° (*c* 0.26); NMR 1.34 ppm (s, C-19 CH_3).

Anal. Calcd for $C_{24}H_{33}ClO_6$: C, 63.64; H, 7.34; Cl, 7.83. Found: C, 63.90; H, 7.09; Cl, 7.89.

21-Chloro-4β,5-epoxy-9-fluoro-11β-hydroxy-2',2'-dimethyl-5β-pregnano[16α,17-*d*][1,3]dioxolane-3,20-dione (2b). A solution of 30 g of **1b** ([α]D +156°, *c* 0.73) in 3 l. of methanol was stirred with 72 ml of 30% hydrogen peroxide and 48 ml of 4 N sodium hydroxide solution for 4 days and poured into 36 l. of water, and the resulting solid filtered. This was combined with three identical batches and chromatographed on silica gel to give a total of 60.11 g of **2b** and 30.4 g of recovered **1b**. A similar sample of **2b** had mp 254–256 °C from ethanol–water; [α]D +146.5° (*c* 0.24); NMR 1.40 ppm (s, C-19 CH_3).

Anal. Calcd for $C_{24}H_{32}ClFO_6$: C, 61.21; H, 6.85; Cl, 7.53; F, 4.03. Found: C, 61.48; H, 6.75; Cl, 7.30; F, 3.91.

Similar experiments worked up by extraction gave no TLC or NMR evidence for the presence of a second epoxide or any other nonacidic compound.

3β-(Acetyloxy)-21-chloro-9-fluoro-11β-hydroxy-2',2'-dimethylpregn-4-eno[16α,17-*d*][1,3]dioxolan-20-one (4b). A solution of 1.83 g (0.004 mol) of **1b** in 200 ml of methanol was stirred for 1 h at room temperature with 2.2 equiv of sodium borohydride. After the usual workup the product was acetylated with 10 ml of pyridine and 5 ml of acetic anhydride overnight. The reaction mixture was poured into ice–water, stirred for 1 h, and filtered to give 2.1 g of solid. Purification by preparative TLC with chloroform as the developing solvent gave 738 mg (37%) of **4b**, mp 218–220 °C dec from methanol, [α]D +80.0° (*c* 1.6).

Anal. Calcd for $C_{26}H_{36}ClFO_6$: C, 62.58; H, 7.27; Cl, 7.11. Found: C, 62.64; H, 7.01; Cl, 6.91.

21-Chloro-9-fluoro-3β,11β-dihydroxy-2',2'-dimethylpregn-4-eno[16α,17-*d*][1,3]dioxolan-20-one (5b). A solution of 500 mg of **4b** in 80 ml of methanol and 20 ml of tetrahydrofuran was stirred for 1 h under nitrogen with 10 ml of 10% potassium carbonate solution, and then diluted with water and extracted with chloroform to give 455 mg of crude product. Preparative TLC twice with chloroform as the developing solvent followed by crystallization from benzene–hexane gave **5b**: mp 182–184 °C dec; [α]D +101° (c 0.746); NMR 5.41 ppm (broad s, width at half-height = 5 Hz, C-4 H).

Anal. Calcd for $C_{24}H_{34}ClFO_5$: C, 63.10; H, 7.50; Cl, 7.76; F, 4.16. Found: C, 63.40; H, 7.49; Cl, 7.62; F, 4.08.

21-Chloro-4β,5-epoxy-9-fluoro-2',2'-dimethyl-5β-pregnano[16α,17-*d*][1,3]dioxolane-3,11,20-trione (7). A solution of 200 mg (0.0044 mol) of **4b** in 10 ml of dichloromethane was stirred for 1 h with 100 mg (0.005 mol) of 85% *m*-chloroperbenzoic acid. After the usual workup a solution of the product in 25 ml of acetone was stirred with excess Jones reagent for 1.5 h. The usual workup gave a crude product that crystallized from methanol to give 139 mg (70%) of **7**, mp 202–204 °C.

Anal. Calcd for $C_{24}H_{30}ClFO_6$: C, 61.47; H, 6.45; Cl, 7.56; F, 4.05. Found: C, 61.53; H, 6.26; Cl, 7.51; F, 4.09.

Oxidation of 240 mg of **2b** as above gave 145 mg (60%) of **7**, mp and mmp with material from above 202–204 °C.

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Registry No.—**1a**, 630-44-4; **1b**, 3093-35-4; **2a**, 56896-66-3; **2b**, 56896-63-0; **4b**, 60646-27-7; **5b**, 60646-28-8; **7**, 60646-29-9.

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The Association Constants of Organic Complexes of Iodine. A Competitive Equilibrium Study[1]

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Since Benesi and Hildebrand first studied the benzene–iodine complex,[2] many other organic complexes of iodine have been investigated in carbon tetrachloride. Andrews and Keefer have studied complexes of organic halides,[3] polymethylbenzenes,[4] and alkylbenzenes,[5] Tamres, Virzi, and Searles studied iodine complexes of alkylbenzenes.[6] Fluorobenzenes and fluorotoluenes were studied by Tamres,[7] and the iodine complex of benzonitrile was studied by Klaboe.[8] The complexes of polynuclear aromatics have been investigated by Bhattachara and Basu,[9] Peters and Person,[10] Blake, Winston, and Patterson,[11] and de Maine and Peone.[12] The association constants for all these complexes were found using ultraviolet spectroscopy and usually a modification of the Benesi–Hildebrand equation, such as the Scott equation.[13]

In this investigation the association constants were measured by a different technique. In the iodine–alkene addition reaction the position of the equilibrium is dependent on the nature of the solvent system.[14] A very convenient reaction to study is to determine the effects of a donor in the position of equilibrium in the cyclohexene–iodine addition reaction. A solution of 0.064 M cyclohexene and 0.032 M iodine in carbon tetrachloride reacts to 61.6% completion at 25.0 °C. A donor compound was added to the carbon tetrachloride solvent, generally to make a 1.0 M solution of the donor. The difference in the cyclohexene–iodine reaction in pure carbon tetrachloride and in the carbon tetrachloride–donor solvent system was used to determine the association constant of the complex formed. Assuming that only a 1:1 complex is formed, the association constant for the donor–iodine complex can be determined using eq 1.[15]

$$K_{sd} = \frac{X_1 (S - d + X_1/K_a (b - X_1))}{K_a(b - X_1)d - X_1} \qquad (1)$$

K_a = equilibrium constant for I_2 addition to cyclohexene no donor in solvent)

X_1 = concentration of I_2 reacted = concentration of alkene reacted = concentration of diiodoalkane formed

S = initial concentration of donor

a = initial concentration of iodine

b = initial concentration of cyclohexene

Table I. Association Constants for the Iodine Complexes of Organic Compounds in Carbon Tetrachloride at 25.0 °C

Registry no.	Compd	l, mol^{-1} This work	Lit.
1772-22-1	Benzene	0.175 ± 0.006	0.15,[a,b,d] 0.17[c]
	Polyalkylbenzenes		
2789-26-6	*o*-Xylene	0.29 ± 0.001	0.27[a]
2605-03-0	*m*-Xylene	0.33 ± 0.005	0.31[a]
2768-91-4	*p*-Xylene	0.30 ± 0.004	0.31,[a] 0.32[b]
2605-05-2	1,2,5-Trimethylbenzene	0.55 ± 0.02	0.82,[a] 0.63[b]
2768-93-6	1,2,3,4-Tetramethylbenzene	0.78	
60978-40-7	1,2,4,5-Tetramethylbenzene	0.64	
2603-90-9	Pentamethylbenzene	0.82 ± 0.03	0.88,[a] 0.94[e]
24317-90-6	Hexamethylbenzene	1.29 ± 0.03	1.35,[a] 1.52,[b] 1.48[c]
	Monoalkylbenzenes		
2605-02-9	Methylbenzene	0.25 ± 0.003	0.16,[a] 0.15[f]
39573-42-7	Ethylbenzene	0.23 ± 0.003	
60944-81-2	Propylbenzene	0.23	
60944-83-4	Butylbenzene	0.19	
60978-41-8	Pentylbenzene	0.20	
60978-42-9	Hexylbenzene	0.17	
60978-43-0	Heptylbenzene	0.17 ± 0.01	
60944-82-3	Isopropylbenzene	0.25	
60944-85-6	*tert*-Butylbenzene	0.24	
60978-44-1	Cyclohexylbenzene	0.24	
	Substituted Benzenes		
60978-45-2	Nitrobenzene	0.03	
2649-27-6	Benzonitrile	0.28	0.8[g]
1650-58-4	Fluorobenzene	0.06	
3879-17-2	Chlorobenzene	0.07	
3797-16-8	Bromobenzene	0.11 ± 0.01	0.13[a]
4015-94-5	Iodobenzene	0.34	
60978-46-3	*o*-Dichlorobenzene	0.00	
60978-47-4	Trifluoromethylbenzene	0.00	
	Aliphatic Compounds		
31036-98-3	Hexane	0.03	
18681-91-9	Methylcyclohexane	0.04	
60978-48-5	1-Chlorobutane	0.11	
60978-49-6	Chlorocyclohexane	0.15	
58993-03-6	1-Bromopropane	0.27 ± 0.013	
60978-50-9	2-Bromopropane	0.33 ± 0.05	
58992-99-7	Iodomethane	0.67	
58993-00-3	Iodoethane	0.82	0.29[f]
58993-01-4	1-Iodopropane	0.79	
58993-02-5	2-Iodopropane	0.77	
60978-51-0	Tetrachloroethane	0.00	
	Polynuclear Aromatics		
60978-52-1	Biphenyl	0.26	0.37[h]
60978-53-2	Acenaphthene	0.42	
26977-60-6	Phenanthrene	0.24 ± 0.03	0.15,[a] 0.45,[i] 1.06[h]
13531-66-3	Naphthalene	0.24 ± 0.01	0.25,[a] 03,57,[j] 0.62[k]
60978-54-3	1-Nitronaphthalene	0.06	

[a] Reference 4. [b] Reference 5. [c] Reference 2. [d] reference 7. [e] Reference 6. [f] Reference 3. [g] Reference 8. [h] Reference 9. [i] Reference 10. [j] Reference 11. [k] Reference 12.

$d = a - X_l$

K_{sd} = dissociation constant

K_s = association constant = $1/K_{sd}$

When the association constant was experimentally determined a minimum of four times for a particular complex, the uncertainty was computed using Student's method at 90% confidence limit.[16] All complexes were done at least in duplicate. Although the uncertainty may indicate more significant figures, to ensure the reliability of this data the association constants are reported to only two decimal places with the exception of benzene. The benzene–iodine complex was run a number of times, and the value reported here agrees well with literature values for the association constant.

As the reviewers of this paper have correctly pointed out, this derivation does assume that the association constant of the iodine cyclohexene charge transfer complex is small enough to be ignored. An estimate of the association constant

for the cyclohexene iodine complex shows that the error from this assumption is small and within the confidence limits given. Moreover, kinetic work we have done on olefin systems indicates that at least part of the charge transfer complex between cyclohexene and iodine yields the diiodoalkane upon quenching in KI/H_2O.

Results and Discussion

The association constant for the benzene–iodine complex has been measured by several people, and the values found in the literature agree with the value reported in this work (Table I). The values reported here for the xylene complexes are also very close to the values reported in the literature, although there is a slight discrepancy in the order of the xylenes. This work indicates that the *m*-xylene has the greatest complexing ability with iodines. There is considerable disagreement in the literature on the value for the association constant of the 1,3,5-trimethylbenzene complex, but this work does agree with one of the values reported by Andrews and Keefer.[5] One would expect, since the methyl group is an electron donor, that the aromatic ring would become an increasingly better donor as more methyl groups are attached. This work agrees with such predictions as well as with the values reported in the literature for the polymethylbenzene complexes.

Toluene has the largest K_a value for any monoalkylbenzene. Longer alkyl groups probably sterically interfere with the approach of the iodine causing association constants which are less than that of toluene.

The association constants for other substituted benzenes are also determined. Nitrobenzene is a poor iodine complexer, which is expected from the electron-withdrawing properties of the nitro group. Surprisingly, although the cyano group is deactivating, benzonitrile is a relatively good complexer. Apparently the lone pair of electrons on the nitrogen are available for n-type complex formation with iodine. The halogens also deactivate the ring, but they, like nitrogen, have lone pair electrons. As the size of the halogen is increased, these lone pair electrons become more available for n-type complex formation. Two chloro groups on the ring deactivate the system so that essentially no complex can form, neither π nor n type.

Since the halogens have lone pair electrons, the aliphatic halides have the potential for n-type complex formation. Again the size of the halogen is controlling factor in the availability of the lone pair electron. One observes that the haloaliphatic compounds are better complexers than the corresponding halobenzene compounds.

Although Bhattachara and Basu indicated that biphenyl was twice as good a complexer as benzene,[9] this study indicates that it is not. In fact, it seems to be only one and a half times better than benzene. The spectrophotometric determination of the association constant for phenanthrene is difficult. Peters and Person discussed the difficulties involved in the determination of the value for phenanthrene,[10] and the wide range in values reported in the literature certainly supports their view. This method avoids these difficulties, and, as shown in Table I, it appears that phenanthrene has essentially the same complexing ability as naphthalene. The value reported in this work for naphthalene agrees with literature values. It is interesting that a deactivating group, such as the nitro group, deactivates both rings in naphthalene for π complex formation.

Although an older, less sophisticated technique was used, the results of this investigation do fit the current concepts of organic complexes. Often difficulties arise in studying the complexes spectrophotometrically. In the iodoethane complex, for example, Andrews and Keefer were forced to work on the shoulder of the ultraviolet absorption curve, where error is maximized.[3] Absorption of the starting materials in the region of interest also may cause serious problems. This method avoids such problems. It seems that in some cases titration is the preferable method. Besides reducing the number of problems involved in the determination, this method has added advantage in that several different donors may be studied at the same time under exactly the same conditions. Although the numerical values for the association constants may vary somewhat because of slight variations in conditions, the relative order of the values does not vary. Thus, this study has been able to compile the longest and most self-consistent list of association constants for the organic complexes of iodine. Further research is currently in progress at this laboratory to determine the correlation between complexing ability and reactivity of aromatic compounds.

Experimental Section

The chemicals used were purchased as 99.9% pure or were purified and physical properties checked by conventional procedures. All equilibria were measured at 25.0 ± 0.05 °C. The equilibrium constant for the reaction of iodine with cyclohexene was determined for a solution 0.0640 M in cyclohexene and 0.0320 M in iodine in the solvent carbon tetrachloride. Along with each determination of the equilibrium between cyclohexene and iodine, identical mixtures containing added donor compounds were simultaneously run in order to obtain the K_a values of the donor compounds. In a typical run 2.025 g of iodine was dissolved in carbon tetrachloride to give 100 ml. A total of 1.3145 g of freshly distilled cyclohexene was also made up to 100 ml with carbon tetrachloride. After equilibration at 25.0 °C, 10 ml each of the iodine and alkene solutions were pipetted into 25-ml volumetric flasks. To six such flasks were added the following donors: (1) no donor, blank; (2) 1.9528 g of benzene; (3) 3.075 g of 2-bromopropane; (4) 2.303 g of toluene; (5) 2.655 g of ethylbenzene; and (6) 5.310 g of *p*-xylene. The solutions were made up to 25 ml with solvent and allowed to react at 25.0 °C. Solutions prepared in this manner were 0.0320 M in iodine, 0.0640 M in cyclohexene, and 1.00 M in donor, except for the *p*-xylene which was 2.00 M. Aliquots were titrated in triplicate after 48, 72, and 96 h. For the 2.00-ml aliquots of the above samples the milliliters of 0.0500 M thiosulfate required for the blank and the donor solutions, and the K_a calculated for the donors follow: blank, 0.704; benzene, 0.776, K_a = 0.175; 2-bromopropane, 0.830, K_a = 0.320; toluene, 0.802, K_a = 0.250; ethylbenzene, 0.796, K_a = 0.232; and *p*-xylene, 0.922, K_a = 0.296.

The K_a for each donor was determined at least twice from separate runs. The three xylene isomers, naphthalene, and phenanthrene were simultaneously run a number of times so as to check their relative K_a values. Although the absolute K_a values might vary slightly from one determinations to another, the order of complexing ability of the xylenes was always meta > para > ortho, and the values for naphthalene and phenanthrene were always identical within experimental error. While laboratory light in many cases accelerated the rate of obtaining equilibrium, it had no apparent effect on the value of K_a.

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(1) (a) Presented in part at the Eighth Great Lake Regional Meeting of the American Chemical Society, Purdue University, June 1974, Abstract No. 193. (b) Taken in part from the B.S. Thesis of P. D. Clark, Bradley University, 1974. (c) Supported in part by a grant from the Research Corporation.
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Thallium in Organic Synthesis. 45. Synthesis of Aromatic Fluorides[1]

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Many useful procedures have been described for the direct monochlorination, -bromination, and -iodination of aromatic compounds;[2-4] there is, however, no general, practical method available for controlled monofluorination. Procedures based on the use of reagents such as elemental fluorine,[5-9] interhalogen halides,[6,10,11] high-valency metal fluorides,[6,12] or xenon difluoride[13,14] are often difficult and dangerous to carry out, usually require specialized apparatus, and usually give complex mixtures of products. Electrolytic methods are equally unattractive.[6,15] The only two generally useful methods for the introduction of fluorine into an aromatic nucleus are nucleophilic displacement of activated halogen and alkoxy groups[16,17] and the Balz–Schiemann reaction.[18-20]

Arylthallium(III) compounds of the type $ArTlX_2$ are attractive and versatile intermediates for the regiospecific synthesis of a wide range of functionalized aromatic compounds,[21-24] including chlorides,[25] bromides,[25,26] and iodides.[25,27] We now describe the preparation of aromatic fluorides from arylthallium(III) difluorides which are readily available in excellent yield by the simple, two-step procedure summarized in eq 1.[28]

$$ArH \xrightarrow{TTFA} ArTl(OCOCF_3)_2 \xrightarrow{KF} ArTlF_2 \qquad (1)$$

We began our investigation by briefly examining the thermal and photochemical stability of arylthallium(III) difluorides. Certain $ArTlX_2$ compounds are known to decompose thermally as outlined in eq 2;

$$ArTlX_2 \xrightarrow{\Delta} ArX + TlX$$
$$X = I, Br, CN, SCN \qquad (2)$$

the temperatures necessary, however, vary from approximately 0 °C for X = I to 228 °C for X = CN.[29] Arylthallium(III) difluorides slowly decompose when heated above 200 °C giving the corresponding hydrocarbons in modest yields; pyrolysis of 4-ethylphenylthallium(III) difluoride at 250–300 °C, for example, gave ethylbenzene (41%) as the only identifiable product. The photolysis of other arylthallium(III) compounds yields aryl nitriles,[22,30] aryl thiocyanates,[31] and biphenyls.[32] However, photolysis of phenylthallium(III) difluoride in aqueous potassium fluoride solution at 253.7 nm did not yield fluorobenzene, and phenylthallium(III) difluoride was recovered unchanged. Neither approach was studied further.

We then examined methods for the preparation of arylthallium(III) bis(tetrafluoroborates), $ArTl(BF_4)_2$, in the expectation that these compounds would decompose in the desired manner, but at moderate temperatures. There are three obvious methods for the preparation of arylthallium(III) bis(tetrafluoroborates): (a) direct thallation of aromatic compounds with $Tl(BF_4)_3$; (b) treatment of arylthallium(III) bis(trifluoroacetates) with sodium tetrafluoroborate; and (c) reaction of arylthallium(III) difluorides with boron trifluoride. We have been unable to investigate method a thus far as all attempts to prepare the requisite thallating reagent failed.

Table I. Preparation of Aromatic Fluorides

$$ArH \xrightarrow{TTFA} ArTl(OCOCF_3)_2 \xrightarrow{KF} ArTlF_2 \xrightarrow{BF_3} ArF$$

Ar	Yield, %[a]	Bp, °C
4-$CH_3C_6H_4$	50	115–120
4-$C_2H_5C_6H_4$	48	140–141
2,4-$(CH_3)_2C_6H_3$	67	140–147
2,5-$(CH_3)_2C_6H_3$	54	140–147
2,4,6-$(CH_3)_3C_6H_2$	71	72–80 (32 mm)
4-$C_6H_5C_6H_4$	45	mp 59–61

[a] Overall yield from ArH to ArF; all yields refer to isolated, distilled, or recrystallized material. No attempt was made to optimize yields.

Method b was unsuccessful; arylthallium(III) bis(trifluoroacetates) do not undergo ligand exchange effectively when treated with aqueous ethanolic solutions of sodium tetrafluoroborate. Investigation of method c, however, led to the development of a convenient procedure for the direct conversion of certain arylthallium(III) difluorides into the corresponding aromatic fluorides.

Passage of boron trifluoride through a cold, stirred suspension of the arylthallium(III) difluoride in either petroleum ether or cyclohexane followed by warming of the reaction mixture gave the aromatic fluoride directly; experimental data for a number of conversions are listed in Table I. The yields of aromatic fluorides prepared by this simple, three-step procedure are moderate and roughly comparable to those reported for the preparation of the same compounds from aryl amines by the Balz–Schiemann reaction. The latter process, while more complicated, is more general than the arylthallium(III) difluoride route which is limited to aromatic substrates which contain neither powerful electron-withdrawing groups nor oxygen or amino substituents. Arylthallium(III) difluorides which do contain such substituent groups give negligibly low yields of aryl fluorides. It should be noted, however, that the arylthallium(III) difluoride route avoids the use of aryl amines and their nitro precursors, many of which are potent carcinogens.

We have not studied the mechanism of the reaction between arylthallium(III) difluorides and boron trifluoride, but formation and subsequent decomposition of arylthallium(III) bis(tetrafluoroborates) is a reasonable hypothesis. Many inorganic fluorides react readily with boron trifluoride to give tetrafluoroborate salts,[33] and arylthallium(III) difluorides, which are known to be ionic,[28] would be expected to react analogously.

Experimental Section

General Procedure for the Preparation of Aromatic Fluorides. Dry, finely powdered arylthallium(III) difluoride (0.05 mol)[28] was added to 150 ml of reagent-grade cyclohexane contained in a 500 ml, three-necked Morton flask fitted with a gas inlet tube, a reflux condenser protected by a drying tube, and a mechanical stirrer with a bearing. The mixture was stirred vigorously and cooled in an ice bath, and boron trifluoride gas was bubbled through the suspension for 1 h (effluent boron trifluoride was trapped in dilute ammonium hydroxide). The boron trifluoride inlet was then removed, and the mixture was heated under reflux for 2 h. The cooled reaction mixture was filtered to remove insoluble salts and the filter cake washed with cyclohexane. Solvent was removed by careful distillation at atmospheric pressure through a 30 × 1.5 cm Vigreux column and the residual oil or solid distilled or recrystallized; experimental data are given in Table I.

Registry No.—ArH (Ar = 4-$CH_3C_6H_4$), 108-88-3; ArH (Ar = 4-$C_2H_5C_6H_4$), 100-41-4; ArH (Ar = 2,4-$(CH_3)_2C_6H_3$), 108-38-3; ArH (Ar = 2,5-$(CH_3)_2C_6H_3$), 106-42-3; ArH (Ar = 2,4,6-$(CH_3)_3C_6H_2$), 108-67-8; ArH (Ar = 4-$C_6H_5C_6H_4$), 92-52-4; $ArTlF_2$ (Ar = 4-$CH_3C_6H_4$), 60705-27-3; $ArTlF_2$ (Ar = 4-$C_2H_5C_6H_4$), 60705-28-4; $ArTlF_2$ (Ar =

2,4-$(CH_3)_2C_6H_3$), 27675-05-4; $ArTlF_2$ (Ar = 2,5-$(CH_3)_2C_6H_3$), 29396-64-3; $ArTlF_2$ (Ar = 2,4,6-$(CH_3)_3C_6H_2$), 27675-11-2; $ArTlF_2$ (Ar = 4-$C_6H_5C_6H_4$), 60705-29-5; ArF (Ar = 4-$CH_3C_6H_4$), 352-32-9; ArF (Ar = 4-$C_2H_5C_6H_4$), 459-47-2; ArF (Ar = 2,4-$(CH_3)_2C_6H_3$), 452-65-3; ArF (Ar = 2,5-$(CH_3)_2C_6H_3$), 696-01-5; ArF (Ar = 2,4,6-$(CH_3)_3C_6H_2$), 392-69-8; ArF (Ar = 4-$C_6H_5C_6H_4$), 324-74-3.

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Highly Strained Ring Systems. Hydrolysis of Tricyclo[4.1.0.0^{2,7}]hept-3-yl Derivatives. Evidence for Participation of Bicyclo[1.1.0]butane Ring

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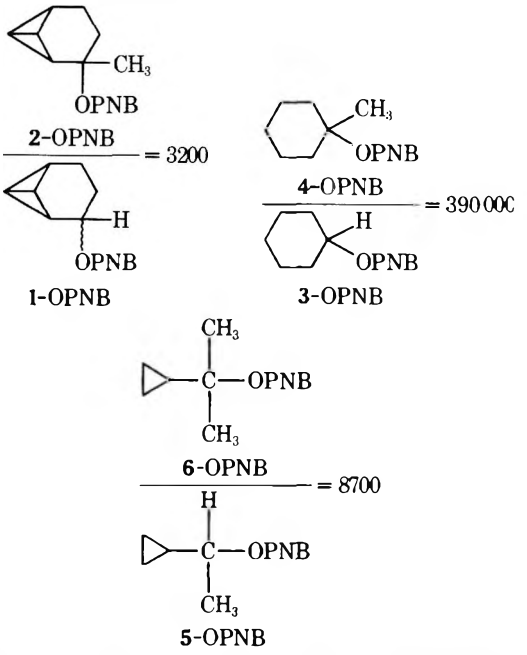
Preparation and studies of strained ring compounds have long intrigued organic chemists. Especially bicyclo[1.1.0]-butane, which has the highest strain energy in bicyclic ring systems, has provided many interesting aspects as regards relationships between strain energy and reactivity.[1] However, only a few solvolytic studies with bicyclo[1.1.0]butane derivatives have been reported.[2] Thus, we synthesized tricyclo[4.1.0.0^{2,7}]hept-3-yl and 3-methyltricyclo[4.1.0.0^{2,7}]-hept-3-yl *p*-nitrobenzoates (1-OPNB and 2-OPNB, respectively), and investigated their solvolytic reactivity in order to determine whether the tricyclo[4.1.0.0^{2,7}]hept-3-yl carbonium ion is a nonclassical ion by bicyclobutane ring participation or a classical ion associated with a relief of its ring strain.

Synthesis of the parent tricyclic ketone was carried out as described in the literature.[3] Treatment of this ketone with sodium borohydride or methyllithium gave alcohol 1-OH or 2-OH, wihch was converted to its corresponding *p*-nitrobenzoate 1-OPNB (mp 92.0–93.0 °C) or 2-OPNB (mp 79.5–80.5 °C) in the usual fashion.

The hydrolysis rates of 1-OPNB and 2-OPNB were measured in aqueous acetone mixtures by titrating the liberated *p*-nitrobenzoic acid displaying nice first-order behavior. The kinetic data are summarized in Table I with literature values for related compounds.

The *p*-nitrobenzoate (1-OPNB) undergoes hydrolysis at a rate 5×10^7 times faster than does cyclohexyl *p*-nitrobenzoate (3-OPNB), while the rate of 1-OPNB is essentially the same as that of methylcyclopropylcarbinyl *p*-nitrobenzoate (5-OPNB). It has been suggested that an α-CH_3/H rate ratio in solvolysis reaction of a charge-delocalized system would decrease when compared to that of a charge-localized system.[4] Thus a rate ratio of 2-OPNB/1-OPNB was compared to that of 4-OPNB/3-OPNB (a charge-localized system), as well as that of 6-OPNB/5-OPNB (a charge-delocalized system). As seen in Table I, the rate ratio of 2-OPNB/1-OPNB exhibits approximately the same as that of 6-OPNB/5-OPNB within



a factor of 3, whereas it is about 100 times less than that of 4-OPNB/3-OPNB. Consequently, these findings suggest that the importance factor underlying the solvolytic reactivity of 1-OPNB is stabilization of its transition state by assisting in charge delocalization rather than by a relief of angle strain.

Hydrolysis of 1-OPNB gives rise to *anti*-7-norbornenol (7-OH) as an only alcoholic product (89%, GLC analysis).

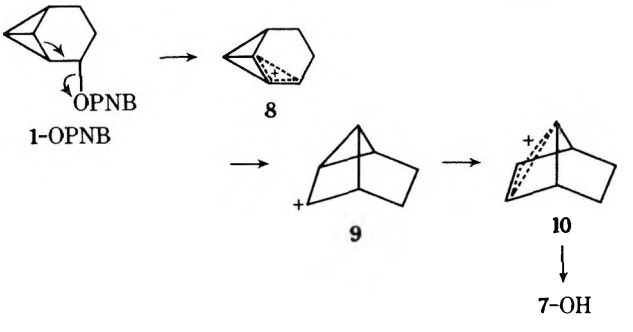


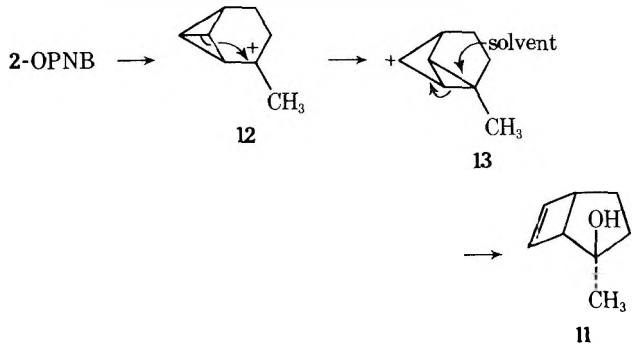
Table I. Kinetic Data for Hydrolysis of Tricyclo[4.1.0.0^{2,7}]hept-3-yl and 3-Methyltricyclo[4.1.0.0^{2,7}]hept-3-yl *p*-Nitrobenzoates (1-OPNB and 2-OPNB, Respectively) and Related Compounds

Registry no.	Substrate	Solvent,[a] %	Temp, °C	k_1, s^{-1}	k_{CH_3}/k_H
60595-06-4	1-OPNB	50	99.8	$(2.96 \pm 0.03) \times 10^{-5}$ [b]	
			80.1	$(4.93 \pm 0.11) \times 10^{-5}$ [b]	
		60	80.1	$(2.26 \pm 0.17) \times 10^{-5}$ [b]	
		80	25	7.03×10^{-9} [c]	
60595-07-5	2-OPNB	60	50.0	$(6.90 \pm 0.09) \times 10^{-4}$ [b]	
			25.0	$(6.05 \pm 0.01) \times 10^{-5}$ [b]	
		65	25.0	$(4.82 \pm 0.09) \times 10^{-5}$ [b]	
		80	25	2.22×10^{-5} [d]	3200
7511-32-2	3-OPNB	80	25	1.41×10^{-16} [e]	
31058-46-5	4-OPNB	80	25	5.48×10^{-11} [f]	390 000
18228-38-1	5-OPNB	80	25	4.28×10^{-9} [g]	
23437-99-2	6-OPNB	80	25	3.75×10^{-5} [h]	8700

[a] Aqueous acetone mixture (v/v). [b] The rates are average values for two independent runs. [c] Extracted from the data at high temperatures and estimated by Grunwald–Winstein equation ($m = 0.56$). [d] Estimated by Grunwald–Winstein equation ($m = 0.30$). [e] Extrapolated from literature data [H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956)] and converted with a factor of $(k_{OPNB,80\%}/k_{OTs,HOAc})_{25°C} = 3 \times 10^{-9}$ [H. C. Brown, M. Ravindrananthan, K. Takeuchi, and E. N. Peters, *ibid.*, **97**, 2899 (1975)]. [f] E. N. Peters and H. C. Brown, *ibid.*, **96**, 263 (1974). [g] Extrapolated from literature data [R. A. Sneen and A. L. Baron, *ibid.*, **83**, 614 (1961)] and converted to 80% acetone by a factor of 6.7 for the solvent change. [h] H. C. Brown and E. N. Peters, *ibid.*, **95**, 2400 (1973).

Although 1-OH is found to be unstable under the solvolysis condition, it does not produce 7-OH. Thus, the formation of 7-OH can be explained as follows: the *p*-nitrobenzoate (1-OPNB) produces bicyclobutonium ion **8** first by an anchimeric assistance of the bicyclobutane ring, and this ion rearranges to tricyclocarbonium ion **9** which leads to 7-OH through a stable bishomocyclopropenyl ion **10**.

On the other hand, hydrolysis of 2-OPNB proceeds with stereospecific rearrangement to *exo*-2-methylbicyclo[3.2.0]-hept-6-en-2-ol (**11**)[5] (71%, GLC analysis) which is not a product from thermolysis of 2-OH, since 2-OH is stable under the solvolysis condition. A possible mechanism for the formation of **11** is that 2-OPNB produces a classical carbenium ion **12** which rearranges to **13** by an interaction of the cationic center with the center bond of the bicyclobutane, and that this ion may give rise to **11** by a concerted process with the bond migration and solvent attack.[6]



Experimental Section[7]

Tricyclo[4.1.0.0^{2,7}]hept-3-yl *p*-Nitrobenzoate (1-OPNB). To a solution of tricyclo[4.1.0.0^{2,7}]hept-3-one[3] (323.9 mg) in 15 ml of methanol was added a solution of sodium borohydride (60.8 mg) in 5 ml of methanol at 0 °C. The resulting solution was allowed to stir at 0 °C for 1.5 h. Then water was added to the solution. After removal of the solvent, the product was extracted with ether three times. The ethereal solution was washed with water, dried ($MgSO_4$), and concentrated to give 234.3 mg (71%) of the crude alcohol (1-OH). Owing to unstability of 1-OH, the NMR spectrum of 1-OH was examined without purification: NMR (CCl_4) δ 3.52 (m, 1 H), 2.58–2.10 (m, 2 H), 1.65 (t, 2 H, J = 2.8 Hz), and 1.48–1.20 (5 H).

To a solution of 1-OH (234.3 mg) in 7 ml of dry pyridine was added *p*-nitrobenzoyl chloride (438.0 mg) in one portion at 0 °C. The resulting solution was allowed to stand in a refrigerator for 2 days, and then poured onto ice–water. The product was extracted with chloroform to give 288.3 mg (52%) of 1-OPNB: mp 92.0–93.0 °C; IR (Nujol) 1731 cm^{-1}; NMR (CCl_4) δ 8.19 (s, 4 H, aromatic), 4.96 (m, 1 H), 2.72 (m, 1 H), 2.43 (m, 1 H), and 1.94–1.02 (m, 6 H).

Anal. Calcd for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05. Found: C, 64.57; H, 5.07.

3-Methyltricyclo[4.1.0.0^{2,7}]hept-3-yl *p*-Nitrobenzoate (2-OPNB). To freshly prepared methyllithium in ether (ca. 27 mmol) was added dropwise a solution of tricyclo[4.1.0.0^{2,7}]hept-3-one (848.7 mg, 7.86 mmol) in 5 ml of ether at room temperature under nitrogen. The resulting solution was stirred for 30 min. Then the excess methyllithium was destroyed with ammonium chloride. Ether extraction gave 3-methyltricyclo[4.1.0.0^{2,7}]hept-3-ol (2-OH) as a clear liquid (619.9 mg, 64%): bp 52–54 °C (6 mmHg); NMR (CCl_4) δ 2.38 (m, 2 H), 2.02 (s, 1 H, OH), 1.67 (t, 2 H, J = 2.4 Hz), 1.58–1.20 (4 H), and 1.10 (s, 3 H, CH_3–).

The alcohol 2-OH (301.2 mg, 2.4 mmol) was converted to its corresponding *p*-nitrobenzoate 2-OPNB as described above for 1-OPNB to yield 104.9 mg (16%): mp 79.5–80.5 °C; IR (Nujol) 1727 cm^{-1} (>C=O); NMR (CCl_4) δ 8.20 (A_2B_2, 4 H, aromatic, $J \approx$ 10 Hz), 3.10 (2 d, 1 H, J = 2.8, 7.0 Hz), 2.46 (m, 1 H), and 1.90–1.30 (9 H).

Anal. Calcd for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53. Found: C, 65.86; H, 5.90.

Kinetic Measurement. The *p*-nitrobenzoates were hydrolyzed in aqueous acetone mixtures (v/v), and the rates were measured as previously described.[8] The kinetic data are shown in Table I.

Solvolysis Product Study. *p*-Nitrobenzoate 1-OPNB (32.2 mg) in 16 ml of 50% aqueous acetone containing 1.4 equiv of sodium bicarbonate was sealed in a test tube under nitrogen and heated for 8 h at 100 °C. The tube was cooled and opened. To the cooled solution was added 8.8 mg of cyclohexanol as an internal standard, and the product extracted with ether–chloroform was analyzed by GLC on a 15% FFAP column at 115 °C to indicate presence of *anti*-7-norbornenol 7-OH (89%) which was identified by GLC and NMR comparisons.

p-Nitrobenzoate 2-OPNB (18.3 mg) was solvolyzed as mentioned above except for being heated in 60% aqueous acetone for 3 h at 50 °C. The GLC analysis using the internal standard showed formation of *exo*-2-methylbicyclo[3.2.0]hept-6-en-2-ol (**11**, 71%), which was identified by GLC and NMR comparisons.

Stability of 1-OH and 2-OH under the Solvolysis Conditions. Alcohol 1-OH (51 mg) in 13 ml of 50% aqueous acetone containing 1.3 equiv of sodium bicarbonate was sealed in a test tube under nitrogen and heated at 100 °C for 7 h. After workup, the crude product was examined by NMR and GLC analyses to indicate formation of bicyclo[3.2.0]hept-6-en-2-one but no observation of 7-OH and 1-OH. On the other hand, 2-OH was found to be stable under the solvolysis condition (60% aqueous acetone, 50 °C, 3 h).

Acknowledgment. We thank Professor K. Kinoshita at S. M. S. for his discussion and encouragement. We are grateful for financial support from Moroyama-Kai and the Ministry of Education, Japan.

Registry No.—1-OH, 60595-08-6; 2-OH, 60595-09-7; 7-OH, 694-70-2; **11**, 53585-67-4; tricyclo[4.1.0.0^{2,7}]hept-3-one, 37939-70-1; *p*-nitrobenzoyl chloride, 122-04-3.

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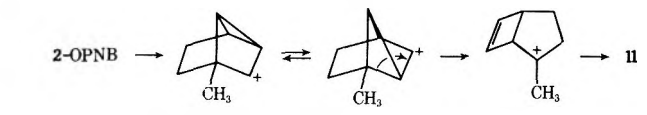
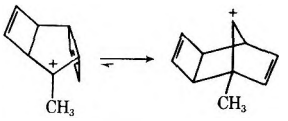
(6) A referee suggested the following alternate mechanism for the formation of **11**.



However, if this mechanism is involved in the hydrolysis of **2**-OPNB, methylnorbornenol would be expected to be a major product (but is not), since a great difference in the stability between the following carbonium ions has been reported.[9]



Thus, we prefer the above mechanism to this alternate one.

(7) Melting points were taken on a Yamato MP-21 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Shimadzu IR-400 spectrophotometer and ultraviolet spectra were determined with a Shimadzu UV-200 spectrophotometer. Nuclear magnetic resonance spectra were recorded using a Hitachi R-24 instrument with chemical shift (δ) given in parts per million downfield from Me_4Si. Gas–liquid chromatography was performed on a Shimadzu GC-4B instrument. Microanalyses were determined in the microanalytical laboratory of the Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan.

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The Role of the Generalized Anomeric Effect in the Conformational Analysis of 1,3-Dioxacycloalkanes. Conformational Analysis of 3,5-Dioxabicyclo[5.1.0]octanes and 3,5,8-Trioxabicyclo[5.1.0]octanes

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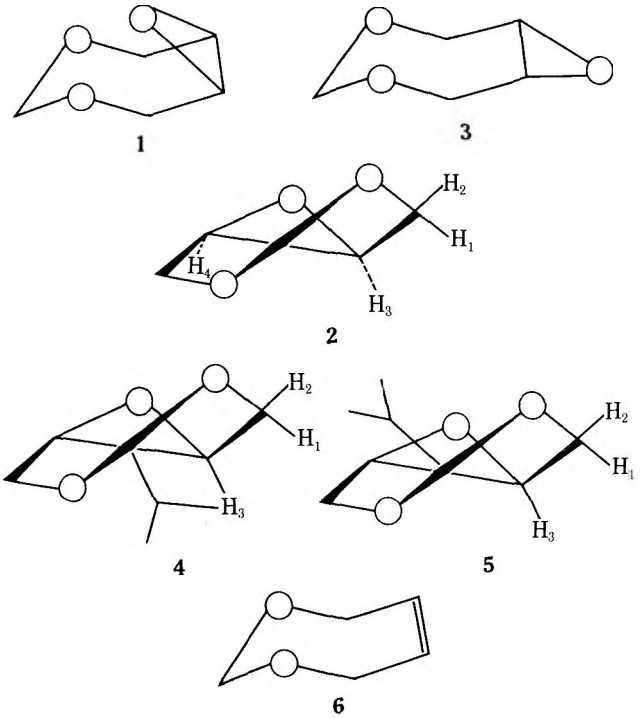
Conformational analysis of 1,3-dioxacycloalkanes has received considerable attention.[1-5] Equilibrium studies on substituted 1,3-dioxacyclopentanes and 1,3-dioxacycloheptanes indicate that numerous low-energy chair conformations, which are interconnected by pseudorotational pathways, are available to an equilibrating pair of diastereoisomers. In contrast 1,3-dioxacyclohexane has only one favorable low-energy chair conformation for each isomer of a cis–trans pair.

Examination of models of 1,3-dioxacycloheptanes reveals that when pseudorotation at C-5,6 is prohibited, only one chair conformation is possible. The pseudorotation pathway of the chair form may be excluded by introduction of a double bond at C-5,6 or by construction of a small ring containing C-5 and C-6. Studies of the conformations for compounds which contain a double bond at C-5,6 indicate that 2,2-dimethyl-1,3-dioxa-5,6-benzocycloheptene,[6] *cis*- and *trans*-4,7-dimethyl-1,3-dioxacyclohept-5-ene, and *r*-2-*tert*-butyl-*c*-4,*t*-7-dimethyl-1,3-dioxacyclohept-5-ene[5] exist in twist-boat conformations.

Our interest in twist-boat conformations in the 1,3-dioxacycloheptenes has led to an investigation of the effect that the construction of a small ring would have on the conformation of these compounds. Recent reports that cycloheptene oxide[7] exists in an equilibrium of two chair conformations and that cycloheptene is also in a chair conformation are of special interest. The conformation of 1,3-dioxacyclohept-5-ene is unsettled.[8] Low-temperature proton magnetic resonance studies failed to indicate line broadening at −120 °C. However, carbon-13 magnetic resonance data strongly suggests that 2,2-dimethyl-1,3-dioxacyclohept-5-ene is in a twist-boat conformation.[5]

It is evident that the epoxide ring does not impart sufficient strain to force cycloheptene oxide into a twist form nor does the double bond make the twist form the more stable conformer for cycloheptene. It seemed probable that 3,5,8-trioxabicyclo[5.1.0]octane (1,3-dioxacyclohept-5-ene oxide) might be more stable in a twist-boat than in a chair conformation. In addition to the strain provided by the epoxide ring an unfavorable interaction due to an anomeric effect[9] could be anticipated for chair conformations **1** and **3** which is relieved in the twist-boat conformation **2**.



The 1,3-dioxacyclohept-5-ene oxide was synthesized by epoxidation of 1,3-dioxacyclohept-5-ene with *m*-chloroperbenzoic acid. The proton magnetic resonance spectrum of this compound remained unchanged in the temperature range 30 to −160 °C. This fact suggested that this molecule might indeed be in a twist-boat conformation. However, it is possible that the coalescence temperature is below −160 °C and that the compound exists as an equilibrium of conformations **1** and **3**.

Supporting evidence for a twist-boat conformation comes from coupling constants for *exo*- and *endo*-2-isopropyl-1,3-dioxacyclohept-5-ene oxide, **4** and **5**, respectively. The endo isomer gave the following coupling constants: $J_{1,2}$ (−13.67),

$J_{1,3}$ (3.78), $J_{2,3}$ (3.79), and $J_{3,4}$ (6.93). The exo isomer gave the following coupling constants: $J_{1,2}$ (−13.99), $J_{1,3}$ (1.13), $J_{2,3}$ (2.99), and $J_{3,4}$ (8.00). Values calculated from the Karplus equation for the chair conformation of the exo isomer with dihedral angles of approximately 155 and 37° were 11 and 7.6 Hz, respectively. Values calculated for the chair conformation of the endo isomer with dihedral angles of approximately 90 and 25° were 2 and 9.3 Hz.[10] It is evident that the experimental values best describe a twist-boat conformation.

Both spectra show evidence of virtual coupling. The spectra were readily reproduced using a LAOCOON III program. The configurational assignments were made on the basis of the chemical shift for the C-2 proton. In the exo isomer this proton lies in the face of the epoxide ring and is expected to give an absorption further upfield than the corresponding proton in the endo isomer. Accordingly that isomer with the C-2 proton chemical shift at 385 Hz was assigned the exo configuration and the isomer with the C-2 proton chemical shift at 411 Hz was assigned the endo configuration.

The construction of the small ring at C(5,6) makes 1,3-dioxacyclohept-5-ene oxide more stable in the twist-boat conformation than in the chair conformation. It is suggested that a combination of the generalized anomeric effect[9] and the strain imposed on the system by the double bond or the epoxide ring results in higher energies for the chair conformations than for the twist-boat conformations.

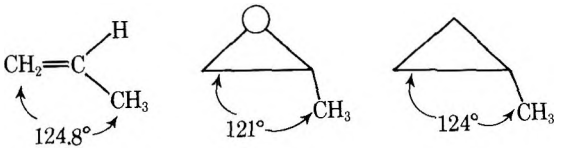
The geometry of the chair conformations for the 1,3-dioxacyclohept-5-enes (6) is such that the C_4–O and the C_7–O bonds are syn periplanar and each of these bonds is in turn syn (and anti) periplanar to the p orbitals of the π bonds. In the twist-boat conformations these bonds and the p orbitals are all oriented gauche. These conformations are predicted by the Wolfe rule which states[11] "When electrons pairs or polar bonds are placed on adjacent pyramidal atoms, syn or anti periplanar orientations are disfavored with respect to that structure which contains the maximum number of gauche interactions".

The geometry of the epoxide molecules is such that the two chair conformations (1 and 3) have C_4–O and C_7–O bonds which are syn periplanar. Conformation 1 has the C_4–O (C_7–O) bonds and the C_5–O (C_6–O) epoxide bonds very close to syn periplanar.

Conformation 3 has the C_4–O (C_7–O) bonds and the C_5–O (C_6–O) epoxide bonds very close to anti periplanar. These bonds are all oriented gauche to each other in the twist-boat conformation (2). This again is consistent with the Wolfe rule.

The reports that cycloheptene[12] and cycloheptene oxide are more stable in chair than in twist-boat conformations indicate that the strain imposed by the double bond or the epoxide ring is not sufficient to raise the energy of the chair conformation above that of the twist-boat. It appears that an additional amount of energy is required to accomplish this, as indicated for the 1,3-dioxacyclohept-5-enes and the 1,3-dioxacyclohept-5-ene oxides. The question remains as to whether the generalized anomeric effect from the 1,3 oxygens alone is sufficient for this purpose or if a more encompassing interaction, as described above, is required.

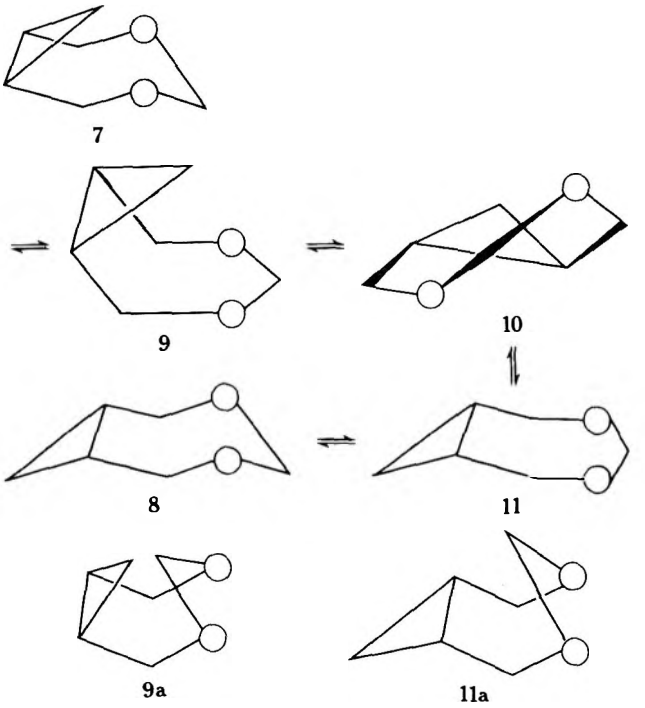
To shed some light on this point we have studied the conformation of 3,5-dioxabicyclo[5.1.0]octane. This molecule has a 1,3-generalized anomeric effect and a source of strain imposed by the cyclopropyl ring. There is, however, no extended generalized anomeric effect. The strain imposed by the cyclopropyl ring is probably not too different from that imposed by the double bonds or the epoxide ring. The values for the bond angles for propylene oxide,[13] propene,[14] and methylcyclopropane[15] are shown below and indicate that the strain created in the corresponding seven-membered rings by bond angle deformation should be similar.



Low temperature proton magnetic resonance spectra indicate that 3,5-dioxabicyclo[5.1.0]octane exists as a mixture of two conformations (7 and 8). It appears that the 1,3-generalized anomeric effect is not of sufficient strength to raise the energy of the chair conformation above that of the twist-boat conformation and that the more generalized anomeric effect is required.

^{1}H NMR Studies. The ^{1}H NMR spectrum at 30° for 3,5-dioxabicyclo[5.1.0]octane gives an AB pattern for the C(4) protons. The chemical shifts are 4.79 and 4.60 ppm downfield from Me_4Si in deuterioacetone solution. At lower temperatures the lines broadened until at −55 °C the spectrum was flat, indicating that the coalescence temperature, T_c, had been reached. At −90 °C the AB pattern had changed into two distinct AX patterns. The chemical shift difference between the averaged chemical shifts of the AX patterns was 34 Hz. An activation energy of 10.7 kcal/mol is calculated from the equation[16] $\Delta G^{\ddagger} = RT_c \ln (2KT_c/h\pi\Delta\delta)$.

This value is larger than the value for cycloheptene oxide (7.9 kcal/mol). Of the possible pathways that can be drawn for the interconversion of the two chair forms, the one that is most attractive is indicated below.



The boat conformations are probably energy maxima for the conversion 9 ⇌ 10, 10 ⇌ 11. Dreiding models show that for conformation 9a the C(4) and C(8) endo hydrogens are in contact position and should represent a very high point on the energy curve. Conformation 11a is analogous to the boat form of cycloheptene, which has been suggested as an energy maximum rather than a local minimum for that conversion process.[17] The interaction between the C(5,6) bond and the C(4) hydrogen should be more severe in this compound than in cycloheptene because the C–O bond distance is shorter than the C–C bond distance. Conformation 9a is probably a very close representation of the transition state for the process 9 ⇌ 10.

Conformations 9 and 11 are such that C(2), C(4), C(6), O(3), and O(5) are in a plane. Since there are no hydrogens in the 3 and 5 positions, the unfavorable energy due to eclipsed hy-

drogens is avoided. This is in contrast to the process suggested for cycloheptene oxide where the conformations analogous to **9** and **11** have six eclipsed hydrogens.

***exo*- and *endo*-4-Isopropyl-3,5-dioxabicyclo[5.1.0]-octanes.** Configurational assignments were made on the basis of coupling constants for the C(1) and C(2) hydrogens and the chemical shift of the C(4) hydrogens. The coupling constants were readily ascertained from the spectra of the pure isomers. The isopropyl group is an effective conformational bias and there was no indication of any conformer other than the indicated chair.

The endo isomer gave coupling constants of $J_{2a-1e} = 1.3$, $J_{2e-1e} = 12.1$, and $J_{2a-2e} = -12.5$ Hz. These values are consistent with values calculated for dihedral angles of 90 and 25°. The exo isomer gave coupling constants of $J_{2a-1a} = 10.0$, $J_{2e-1a} = 6.7$, and $J_{2a-2e} = -12.0$ Hz. These values are consistent with calculated values for dihedral angles of approximately 155 and 37°.

The chemical shift data for the C(2) hydrogens are of special interest. For the endo isomer the C(2a) hydrogen absorption is downfield from that of the C(2e) hydrogen, whereas in the exo isomer the C(2e) hydrogen absorbs downfield from that of the C(2a) hydrogen. The cyclopropyl ring shields the 2a hydrogen more in the exo isomer than in the endo isomer. This is consistent with the configurational assignment since the 2a hydrogen lies in the face of the ring in the endo isomer.

The shielding ability of the cyclopropyl ring provides the basis for the assignment of the axial and equatorial hydrogens at C(4) for the low temperature spectra of 3,5-dioxabicyclo[5.1.0]octane. For conformer **8** the hydrogen which lies in the face of the cyclopropyl ring is axial and is assigned the lower chemical shift value (3.92 ppm); for conformer **7** the equatorial hydrogen is assigned to the 5.14 ppm chemical shift. These assignments are consistent with the fact that equatorial hydrogens absorb at lower field than axial hydrogens in the cyclohexanes.

Equilibration. The *exo*- and *endo*-4-isopropyl-3,5-dioxabicyclo[5.1.0]octanes were equilibrated in refluxing benzene with catalytic amounts of *p*-toluenesulfonic acid. The equilibrium was approached from both sides using samples enriched in one isomer. The ratio endo/exo was 1.2/1 ± 0.03 corresponding to $-\Delta G^{\ddagger} = 0.12$ kcal/mol.

Experimental Section

^{1}H NMR spectra were recorded on a Varian A-60A NMR spectrometer. The low temperature spectra were recorded on a Varian HA 100D spectrometer. Samples were run in deuterioacetone as 10% solutions. All chemical shifts are reported in parts per million downfield from internal Me_4Si. The carbon-13 spectra were recorded at 25.15 MHz on a Varian HA 110D NMR spectrometer interfaced with a Digilab NMR-FTS-3 pulse and data system. The number of data points was 8K or 16K as required to obtain satisfactory resolution. Spectra were recorded with broad band proton decoupling. All chemical shifts are referenced to internal Me_4Si and reported in parts per million. All mass spectra were determined on a AEI-9 high-resolution mass spectrometer. The infrared spectra were recorded on a Beckman IR-8 instrument and the absorption values are reported in microns. *cis*-1,2-Cyclopropanedimethanol was prepared as described in the literature.[18] 1,3-Dioxacyclohept-5-ene and 2-isopropyl-1,3-dioxacyclohept-5-ene were prepared as described in the literature.[19]

3,5-Dioxabicyclo[5.1.0]octane. The general procedure for the preparation of these compounds is that of Bannock and Lappin.[16] The preparation of 3,5-dioxabicyclo[5.1.0]octane is described as a representative example. A mixture of 9.6 g (0.94 mol) of *cis*-1,2-cyclopropanedimethanol, 3.0 g (0.10 mol) of paraformaldehyde, 50 mg of *p*-toluenesulfonic acid, and 100 ml of benzene was refluxed using a Dean-Stark distillation trap. The reaction was terminated when 0.1 mol of water was collected. The mixture was distilled under vacuum and the fraction boiling at 79–81°C (22 Torr) was collected. The yield was 6.1 g (55%): IR (neat) 3.40, 3.50, 6.80, 7.35, 8.70, and 9.20 μ; ^{1}H NMR HC(1,7) 1.30, HC(2,6) 4.28, 3.82, HC(4) 4.79, 4.60, HC(8) 0.80; *m/e* 114 (parent peak); ^{13}C NMR C(1,7) 17.98, C(2,6) 71.55, C(4) 100.59, and C(8) 7.04. The chemical shift values at −90 °C are assigned as follows: CH_a(2,6) 4.22, CH_e(2,6) 3.82, CH_e (4) 5.14, CH_a (4) 4.44 for the conformer **7**. The values for conformer **8** are CH_a (2,6) 3.28, CH_e (2,6) 4.45, CH_a (4) 3.92, CH_e (4) 4.96. The coupling constants for the *endo*- and *exo*-4-isopropyl derivatives are duplicated in the low temperature spectra.

4-Isopropyl-3,5-dioxabicyclo[5.1.0]octanes. The mixture of endo and exo isomers was prepared in 39% yield by reaction of *cis*-1,2-cyclopropanedimethanol and isobutyraldehyde, bp 89–91 °C (22 Torr). The isomers were separated by GLC (8 ft 10% silicone gum rubber, Chromosorb W) and the endo isomer was the first peak: ^{1}H NMR CH_a (2,6) 4.17, CH_e (2,6) 3.85, CH(4) 3.57, C(methyl) 0.88, CH(isopropyl) 1.58; ^{13}C NMR C(4) 114.63, C(2,6) 73.66, C(1,7) 17.45, C(8) 0.85, C(methyl) 16.87, and C(isopropyl) 33.32.

The exo isomer[20] was the second peak: *m/e* 156 (parent peak); ^{1}H NMR CH_a (2,6) 3.10, CH_e (2,6) 4.42, CH(4) 4.10, C(methyl) 0.83, and CH(isopropyl) 1.57; ^{13}C NMR C(4) 112.63, C(2,6) 27.88, C(1,7) 18.39, C(8) 0.58, C(methyl) 17.61, and C(isopropyl) 33.32. The ratio of the areas of the first to the second peak was 1.2/1. Equilibration in refluxing benzene with *p*-toluenesulfonic acid gave the same result.

1,3-Dioxacyclohept-5-ene Oxide. A mixture of 18 g (0.18 mol) of 1,3-dioxacyclohept-5-ene and 40 g (0.23 mol) of *m*-chloroperbenzoic acid in 300 ml of methylene chloride was heated at 40 °C for 96 h. The solution was then cooled and washed with 100 ml of 10% sodium bisulfite solution. The solution was then washed with 5% sodium bicarbonate until all traces of acid were removed. The methylene chloride was evaporated under reduced pressure and the solid that remained was recrystallized from petroleum ether. The yield was 45%; mp 57–58 °C; IR 3.29, 3.35, 3.45, 6.90, 8.40, 9.00, 11.30, 11.50, and 13.75 μ; ^{1}H NMR CH(2) 4.39, 4.76, CH(4,7) 4.06, 4.00, CH(5,6) 4.13; ^{13}C NMR C(2) 97.24, C(4,7) 66.42, C(5,6) 56.47 ppm.

2-Isopropyl-1,3-dioxacyclohept-5-ene Oxide. The procedure for the preparation of this compound was identical with the one described above except that 2-isopropyl-1,3-dioxacyclohept-5-ene was used. The mixture of endo and exo isomers was isolated in 70% yield. The isomers were separated by GLC [12 ft, 5% 1,2,3-tris(cyanoethoxy)propane on Chromosorb]. The first peak was the endo isomer: mp 23–24 °C; ^{1}H NMR CH(2) 4.11, CH(4,7) 4.22, 3.66, CH(5,3) 3.17, CH(isopropyl) 1.79, and CH_3(isopropyl) 0.83; ^{13}C NMR C(2) 110.40, C(4,7) 65.22, and C(5,6) 55.96, C(tertiary isopropyl) 30.98 and C(methyl) 17.88 ppm; IR 3.28, 3.35, 3.45, 6.95, 8.50, 9.10, and 11.30 μ. The exo isomer was the second peak: mp 51–52 °C; ^{1}H NMR CH(2) 3.85, CH(4,7) 4.23, 3.91, CH(5,6) 3.09, CH(isopropyl) 1.68, and CH_3(isopropyl) 0.82; ^{13}C NMR C(2) 110.87, C(4,7) 65.73, C(5,6) 56.61, C(tertiary isopropyl) 32.74, and C(methyl) 17.56 ppm.

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Registry No.—3,5-Dioxabicyclo[5.1.0]octane, 25399-19-3; *cis*-cyclopropanedimethanol, 2345-68-8; paraformaldehyde, 30525-89-4; *endo*-4-isopropyl-3,5-dioxabicyclo[5.1.0]octane, 60595-10-0; *exo*-4-isopropyl-3,5-dioxabicyclo[5.1.0]octane, 60619-53-6; 1,3-dioxacyclohept-5-ene oxide, 286-48-6; 1,3-dioxacyclohept-5-ene, 5417-32-3; 2-isopropyl-1,3-dioxacyclohept-5-ene, 5417-35-6; *endo*-2-isopropyl-1,3-dioxacyclohept-5-ene oxide, 60595-11-1; exo-2-isopropyl-1,3-dioxacyclohept-5-ene oxide, 60619-54-7.

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Metal Hydride Reduction of Bicyclo[2.2.2]octan-2-ones. Preparation and Stereochemistry of 5-Substituted Bicyclo[2.2.2]octan-2-ols

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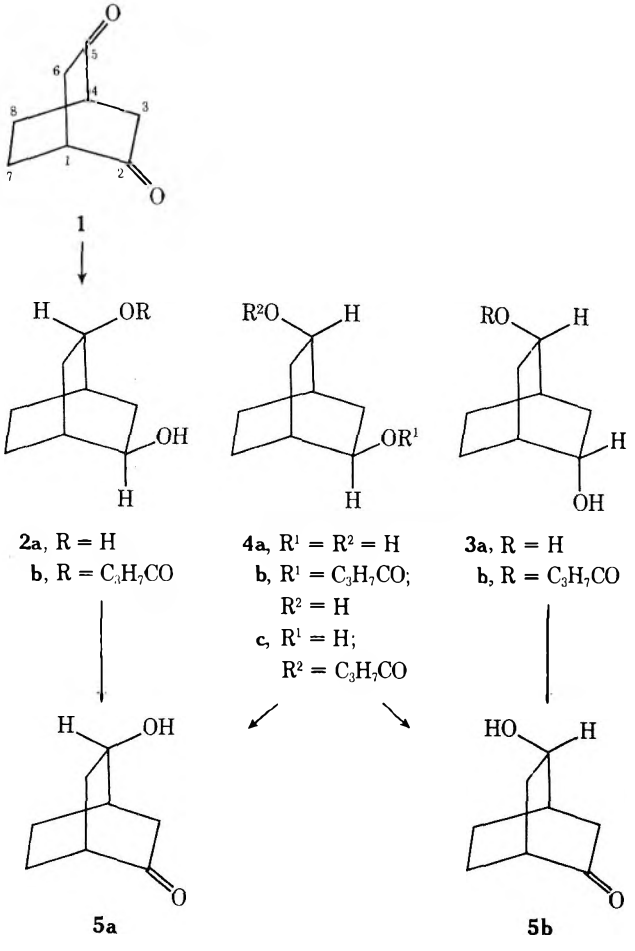
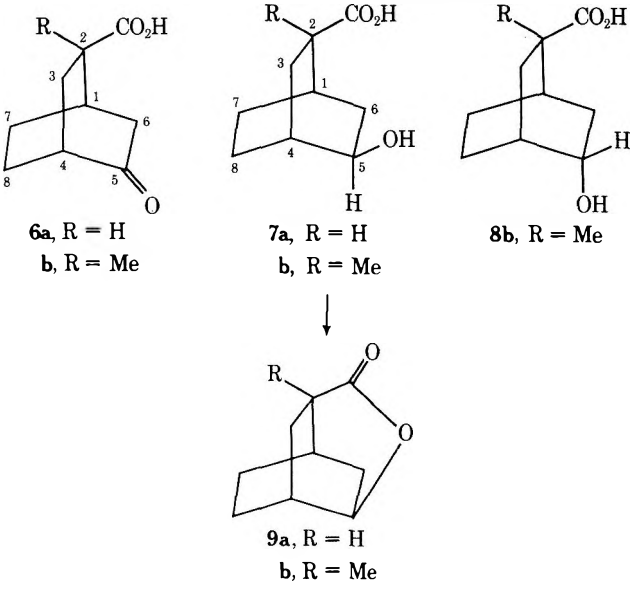
We have examined the metal hydride reduction of a number of 5-substituted bicyclo[2.2.2]octan-2-ones in order to prepare compounds of known relative geometry at the 2,5 position which were required as template molecules for enzyme mimetic studies. Bicyclo[2.2.2]octane-2,5-dione (**1**), prepared by a modification of the method of Guha and Krishnamurthy,[1] was treated with sodium borohydride at room temperature to give a mixture (70–80%) of diols. One isomer could be separated by thin layer chromatography on silica gel, but more satisfactory separation was achieved by either short path column chromatography on alumina[2] or high-pressure liquid chromatography on Porasil. The three diols **2a, 3a,** and **4a** were eluted in that order. The diol **4a** was readily recognized to have the syn-anti configuration of the OH groups, since on partial oxidation it gave two 5-hydroxybicyclo[2.2.2]octan-2-ones and partial esterification with butyryl chloride gave two monobutyrates. The other two isomers each gave a single, different 5-hydroxybicyclo[2.2.2]octan-2-one on oxidation, and each isomer also gave a single, different monobutyrate. The stereoisomers **2a** and **3a** were distinguished from the ^{13}C NMR spectra,[3] and by the ^1H NMR spectra of their respective monobutyrates, taken in the presence of $Eu(DPM)_3$.

The ^1H NMR spectrum of **2b** in $CDCl_3$ with 0.1 equiv of $Eu(DPM)_3$ showed the C-7, C-8 bridge protons appearing in the same region as the β-CH_2 protons of the *n*-butyryl group, these protons thus experiencing only a small downfield shift. By contrast, under the same conditions the C-7, C-8 bridge protons in **3b** were all shifted further downfield, the protons syn to the OH group being more deshielded than those syn to the ester group.[4] The chemical shift of the other protons in the spectra of **2b** and **3b** were also in accord with the stereochemical assignment.

Reduction of **1** with lithium aluminum hydride gave essentially the same composition of diols, but reduction with lithium tri-*tert*-butoxyaluminum hydride gave a mixture comprised almost exclusively of the isomers **3a** and **4a.**

In contrast, reduction of the keto acid **6a** with sodium borohydride gave only one isomer, the known syn alcohol **7a.**[5] However, when the 2-methyl derivative **6b** was reduced under the same conditions, besides the predominant syn isomer **7b,** some of the anti isomer **8b** was also obtained. The assigned stereochemistry of these isomers was confirmed by the conversion of **7a** and **7b** into the respective lactones **9a** and **9b.**





The lack of stereoselective control in the reduction of **1** suggests that there is little preference for the approach of the borohydride to the first ketone group.[6,7] The smaller amount of **2a** compared to **4a** may indicate that the formation of the OH syn to the second ketone group assists in directing the borohydride from that side of the molecule.[8] The syn carboxylic acid group of **6a** presumably shields the ketone function from attack on that side, allowing exclusive formation of **7a.** We suspect that the lower stereoselectivity found in the reduction of **6b** is caused by increased steric shielding from the C-7,8 bridge on the ketone owing to the interaction with the C-2 methyl group, which forces these carbons closer to the C-5,6 bridge.

Experimental Section

^1H NMR spectra ($CDCl_3$) were recorded on either a Varian T-60 or HA-100 spectrometer using Me_4Si as internal standard and are reported in δ units. ^{13}C NMR spectra ($CDCl_3$) were recorded on a

Varian CFT-20 spectrometer with Me_4Si as internal standard and are reported in parts per million. IR spectra were recorded on a Unicam SP-200 spectrophotometer. Mass spectra were taken on either an AEI-MS 9 or MS 12 spectrometer at 70 eV. Aluminium oxide for chromatography was Merck PF_{254} (type E) and Kieselgel was Merck (0.05–0.2 mesh).

Reduction of Bicyclo[2.2.2]octa-2,5-dione. The dione **1** (1.40 g, 10 mmol) was dissolved in ethanol (300 ml), the solution was stirred at room temperature, and sodium borohydride (2.85 g, 7.5 mmol) was added. After 3 h the clear solution was acidified with 20% HCl (100 ml) and then neutralized with Na_2CO_3. The solvent was removed by evaporation and the residual white solid was heated under reduced pressure whereupon a mixture of the diols (1.0 g) sublimed. The mixture was preadsorbed on Kieselgel (100 g), added to a column of Kieselgel (1000 g), and eluted with a mixture of $CHCl_3$–EtOH (9:1 v/v). Compound **2a** (100 mg) eluted first followed by a mixture of **3a** and **4a** (600 mg). The latter mixture was preadsorbed on alumina (15 g), added to a column of alumina (150 g), and eluted with $CHCl_3$–petroleum ether (9:1 v/v). Compound **3a** (300 mg) was eluted first followed by **4a** (150 mg).

Compound **2a:** mass spectrum *m/e* 142 (16%, M^+), 124 (66%, $M^+ - H_2O$); IR (KBr) 3320 (b), 2920, 2858, 1445, 1360 cm^{-1}; ^1H NMR δ 4.0 (m, 2 H), 2.2–1.0 (m, 12 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.85. Found: C, 67.76; H, 9.79.

Compound **3a:** mass spectrum *m/e* 142 (20%, M^+), 124 (40%, $M^+ - H_2O$); IR (KBr) 3280 (b), 2920, 2858, 1440, 1362 cm^{-1}; ^1H NMR δ 4.0 (m, 2 H), 2.2–1.0 (m, 12 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.85. Found: C, 67.70; H, 10.10.

Compound **4a:** mass spectrum *m/e* 142 (1%, M^+), 124 (100%, $M^+ - H_2O$); IR (KBr) 3280 (b), 2920, 2858, 1440, 1365 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.85. Found: C, 67.45; H, 10.09.

A more efficient separation of the mixture of the three diols could be effected by high-pressure liquid–liquid chromatography on Porasil (4.0 ft × 0.375 in.) using MeOH–$CHCl_3$ (3:97 v/v) as eluent. Under these conditions 1.0 g of the mixture gave 100 mg of **2a**, 300 mg of **3a**, and 400 mg of **4a**.

Esterification of 2a, 3a and 4a. The diol (100 mg, 0.7 mmol) was dissolved in dry THF (10 ml) and butyryl chloride (80 mg, 0.74 mmol) was added. The solution was stirred for ca 2 h, the reaction being monitored by TLC (SiO_2) and worked up when the diester was detected (R_f ~0.9, Et_2O). The solvent was removed under reduced pressure and the residue was extracted with ether. Removal of the ether gave an oil which on preparative TLC (SiO_2, Et_2O) gave the monoester (ca. 125 mg, 80%).

Compound **2b:** mass spectrum *m/e* 212 (1%, M^+), 194 (55%, $M^+ - H_2O$); ^1H NMR δ 5.0 (m, 1 H), 4.0 (m, 1 H), 2.6–0.8 (m, 17 H).

Compound **3b:** mass spectrum *m/e* 212 (2%, M^+), 194 (100%, $M^+ - H_2O$); ^1H NMR δ 5.0 (m, 1 H), 4.0 (m, 1 H), 3.0–1.0 (m, 17 H).

Compound **4b,c:** These compounds were distinct on TLC but were not separated from each other. The mixture had mass spectrum *m/e* 212 (1%, M^+), 194 (100%, $M^+ - H_2O$); ^1H NMR δ 5.0 (m, 1 H), 4.0 (m, 1 H), 1.0–3.0 (m, 17 H).

Oxidation of the Diols to the Monoketones. The diol **4a** (100 mg, 0.07 mol) was dissolved in acetone (1.5 ml) and Jones reagent (0.01 N) was added dropwise, the reaction mixture being monitored by TLC (Al_2O_3; Et_2O–$CHCl_3$, 3:2 v/v) after each addition. After complete disappearance of the starting material the reaction mixture was separated by TLC, using the above conditions. TLC showed two compounds, the monoketones **5a** and **5b.** The mixture of **5a,b** had mass spectrum *m/e* 140 (M^+), 122 ($M^+ - H_2O$); IR ($CDCl_3$) 3600, 3400, 2900, and 1740 cm^{-1}. Oxidation of the mixture of monoketones with Jones reagent gave the diketone **1.** Similar oxidation of **2a** gave only the monoketone **5a** (TLC), and oxidation of **3a** gave only the monoketone **5b** (TLC). Both **5a** and **5b** were separately converted into **1** by further oxidation.

Reduction of the Keto Acids 6a and 6b. The keto acid (9.5 g, 52.2 mmol) was dissolved in ethanol (150 ml), the solution was made alkaline with 10% NaOH solution, sodium borohydride (6.0 g, 15.8 mmol) was added in several portions, and the mixture was refluxed for 3 h. The solution was neutralized with 10% HCl solution, the ethanol was removed under reduced pressure, and the residual mixture was extracted with chloroform. The chloroform solution was dried ($MgSo_4$) and the solvent removed by evaporation to give the corresponding alcohols (**6a** → **7a**; **6b** → **7b** + **8b**).

Compound **7a:** 8.1 g, 85%; mp 143–144 °C (lit.[5] 143–144 °C); mass spectrum *m/e* 170.0951 ($C_9H_{14}O_3$ requires 170.0943); ^1H NMR δ 8.40 (s, 2 H, OH, CO_2H), 3.85 (m, 1 H, H-5), 2.8–1.6 (m, 11 H); ^{13}C NMR 180.04 (CO_2H), 68.46 (C-5), 41.47 (C-2), 33.68 (C-6), 31.16 (C-4), 28.55 (C-1), 25.01 (C-7), 22.80 (C-8), 21.28 ppm (C-3).

Compound **7b** (recrystallization from acetone): 66%; mp 167–168 °C; mass spectrum *m/e* 184.1087 ($C_{10}H_{16}O_3$ requires 184.1099), 93 (100%); IR ($CHCl_3$) 3500, 1710 cm^{-1}; ^1H NMR δ 6.50 (s, 2 H, OH, CO_2H), 3.85 (m, 1 H, H-5), 2.8–1.6 (m, 11 H), 1.30 (s, 3 H, CH_3); ^{13}C NMR 182.78 (CO_2H), 68.29 (C-5), 43.44 (C-2), 35.80 (C-6), 33.43, 32.53 (C-1, 4), 30.01 (C-3), 26.28 (Me), 22.76 (C-8), 20.07 ppm (C-7).

Compound **8b** (separated from **7b** by conversion of **7b** to the lactone **9b** (see below): 9%; mp 182–183 °C; mass spectrum *m/e* 184.1089 ($C_{10}H_{16}O_3$ requires 184.1099), 93 (100%); IR ($CHCl_3$) 3500, 1710 cm^{-1}; ^1H NMR δ 6.50 (s, 2 H, OH, CO_2H), 3.85 (m, 1 H, H-5), 2.8–1.6 (m, 11 H), 1.30 (s, 3 H, CH_3); ^{13}C NMR 181.80 (CO_2H), 68.00 (C-5), 42.76 (C-2), 35.53 (C-6), 34.31 (C-3), 33.11, 32.78 (C-1,4), 26.28 (Me), 20.91 (C-7), 17.61 ppm (C-8).

Lactonization of 7a and 7b. The alcohol (300 mg, 176 mmol) was dissolved in dry toluene (benzene for **7b**) (30 ml), a small amount of *p*-toluenesulfonic acid (ca. 10 mg) was added, and the mixture was heated to reflux under N_2 for 2 h. Ether (20 ml) was then added to the cooled solution, and the mixture was then extracted with 10% aqueous $NaHCO_3$ (2 × 5 ml), and then washed with water until the washings were neutral. The organic layer was dried ($MgSO_4$) and evaporation of the solvent gave the lactone.

Compound **9a** (purified by sublimation (13 mm), recrystallization from petroleum ether–benzene): 80 mg, 37%; mp 205–206 °C (lit.[5] 204.5–205.5 °C); mass spectrum *m/e* 152.0843 ($C_9H_{12}O_2$ requires 152.0837); IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 4.5 (m, 1 H, H-5), 3.2–1.6 (m, 11 H); ^{13}C NMR 77.97 (C-2), 40.93 (C-5), 35.26 (C-3), 28.12 (C-6), 26.36 (C-4), 23.78 (C-1), 21.87, 21.52 ppm (C-7,8).

Compound **9b** (purified by sublimation): 195 mg, 71%; mp 124–125 °C; mass spectrum *m/e* 166.0994 ($C_{10}H_{14}O_2$ requires 166.0992); IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 4.65 (m, 1 H, H-2), 3.2–1.6 (m, 11 H), 1.2 (s, 3 H, Me); ^{13}C NMR 76.67 (C-2), 43.00 (C-5), 35.39, 34.95 (C-3,6), 30.69 (C-4), 27.01 (C-1), 21.59 (C-8), 20.51 (C-7), 18.12 ppm (Me).

Acknowledgments. We thank the Science Research Council (U.K.) for support. One of us (D.D.) thanks the Pahlavi Foundation for a grant.

Registry No.—**1**, 57346-05-1; **2a**, 57378-53-7; **2b**, 60662-00-2; **3a**, 57378-52-6; **3b**, 60687-03-8; **4a**, 57346-04-0; **4b**, 60687-04-9; **4c**, 60687-05-0; **5a**, 60662-01-3; **5b**, 60687-06-1; **6a**, 49826-60-0; **6b**, 57346-07-3; **7a**, 41977-18-8; **7b**, 38347-91-0; **8b**, 57378-54-8; **9a**, 49826-59-7; **9b**, 38348-92-1; butyryl chloride, 141-75-3.

References and Notes

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(3) P. J. Garratt and R. Riguera, *J. Org. Chem.*, **41**, 465 (1976).
(4) It is well known that $Eu(DPM)_3$ binds more readily to hydroxyl than to ester functions. See J. K. M. Sanders and D. H. Williams, *J. Am. Chem. Soc.*, **93**, 641 (1971); F. Bohlman and J. Jacob, *Chem. Ber.*, **108**, 2809 (1975).
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(6) Each ketone group in **1** is flanked on one side by a two-carbon methylene bridge and on the other by a bridge consisting of a methylene group and a remote carbonyl group. The steric shielding provided by these bridges would appear to be very similar.
(7) See E. C. Ashby and S. A. Noding, *J. Am. Chem. Soc.*, **98**, 2010 (1976).
(8) However, compound **4a** can be obtained from either the monoketone **5a** or **5b** whereas **2a** can only arise from **5a**, so that without any steric preference twice as much of **4a** should be obtained as **2a** (or **3a**). That there is some direction of the second reduction is supported by the finding that with the more hindered reducing agent no **2a** was formed.

Oxidation of 1,3-Dihydrobenzo[*c*]selenaphene (2-Selenaindan) to 2,2′-Diformyldibenzyl Diselenide

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As part of the development of an alternate synthesis of selenobiotin (Figure 1),[1] we wished to explore the possibilities of α-alkylation of selenoxides lacking β hydrogen: whether they would be stable, and if they would react similarly to

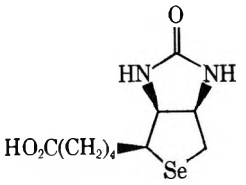
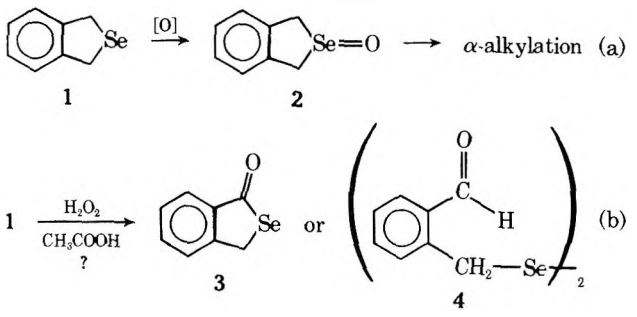


Figure 1. selenobiotin

sulfoxides in α-alkylation reaction.[2] A simplified model compound on which to try this reaction appeared to be 2-selenaindan (1), and so we attempted the first step of Scheme Ia. Since even oxidation at low temperatures with ozone failed

Scheme I



to result in anything but intractable yellow oils with IR and NMR spectra indicating that we had obtained a product or products not including the one in which we were interested at the time, we directed our experimental efforts into other areas.

Our interest was renewed in this reaction when a report appeared[3] that oxidation of 1 with H_2O_2/CH_3CO_2H yielded 2-selenaphthalide (3), Scheme Ib. Physical and spectral properties were attributed to 3, however, which were different from those attributed to 3 synthesized by nonoxidative routes.[4] Furthermore, the controlled oxidation of 1 with a stoichiometric amount of cold H_2O_2 led to a solution of 2 (which is not stable enough to be isolated), which was then converted to benzo[3]selenophene.[5] It was of interest to us to identify the solid reported by Magdesieva and Vdovin as the major product of a nonstoichiometric oxidation of 1.

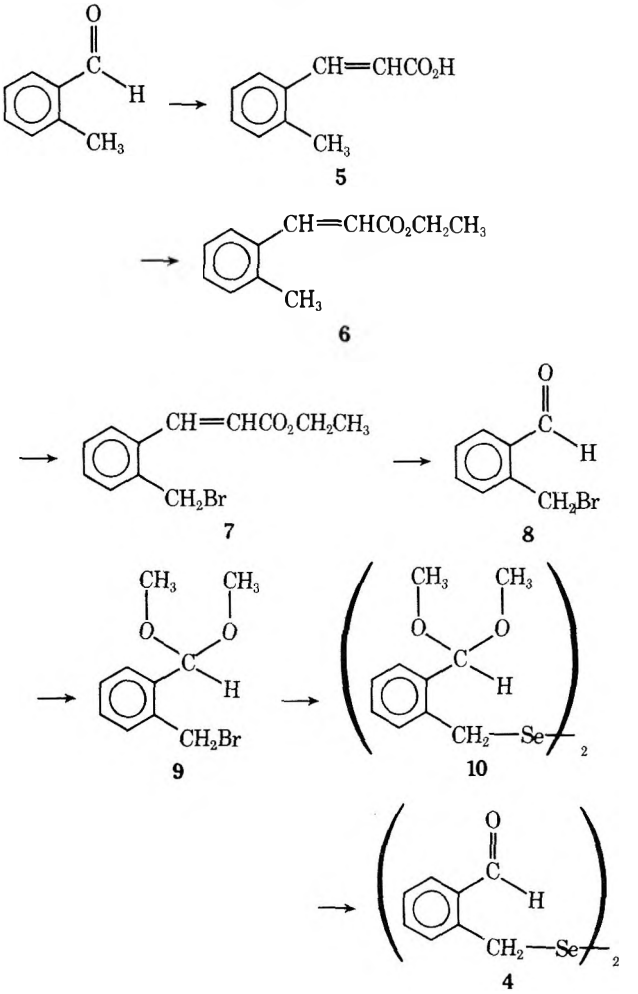
We repeated the oxidation of 1, using the reported[3] H_2O_2/CH_3COOH reagent, and continued to obtain as the major product a viscous yellow oil which did not crystallize, and which presented the same spectroscopic appearance and difficulty in purification which we had previously encountered with ozone oxidation. During all stages of purification, this oil slowly deposited elemental selenium, which has been reported to be characteristic of benzyl diselenides.[6] Spectral and TLC evidence indicated that while the oil was readily purified to better than 90% one component, a purity of greater than 98% was inaccessible by the methods we attempted [the high-purity, highly viscous light-yellow oils (which were used for all recorded spectra determinations) did not crystallize under a vacuum, protected from light]. NMR measurements gave the same two peaks (δ 4.28, singlet, CH_2; δ 7.50, multiplet, aromatic CH) reported by Magdesieva and Vdovin,[3] in the ratio of 4:2. Also, however, there is observed an additional peak at δ 10.1, singlet, relative intensity 1, characteristic of aromatic aldehydes.[7] The infrared spectrum of our oil, and the product reported by Magdesieva and Vdovin, possesses a peak at 1695 cm^{-1}, characteristic of an aromatic aldehyde.[8a] Additional absorptions not reported by Magdesieva and Vdovin, of 2835 and 2740 cm^{-1}, also characteristic of aldehydes,[8b] were found in the IR spectrum of our oil.

In addition, we repeated one of the reported syntheses of 3,[4b] and verified that the IR and NMR features obtained for 2-selenaphthalide are different from those for the yellow oil, and those reported by Magdesieva and Vdovin[3] (Table I).

[It is interesting to note that only the relative electronegativities of O, S, and Se (last column of Table I) need to be invoked to explain the relative chemical shifts of both the aliphatic and aromatic protons in the authentic 2-X-phthalides. It would not be possible to accommodate the reported relative chemical shift of the Magdesieva and Vdovin[2] compound on an electronegativity argument alone.]

On the basis of the spectral data reported in Table I, which are identical except for the aldehyde hydrogen peak in the NMR (δ 10.1), we postulated that oxidation of 1 yields 4, not 3. The reported elemental analysis[3] supports equally well structure 3 or 4 (compound 3, C_8H_6OSe, requires 48.75 C and 3.07 H; compound 4, $C_{16}H_{14}O_2Se_2$, requires 48.26 C and 3.54 H; Magdesieva and Vdovin report 48.6 C and 3.5 H[3]). We have confirmed that 2,2′-diformyldibenzyl diselenide (4) is indeed a product of nonstoichiometric oxidation of 1 by the synthesis indicated in Scheme II.

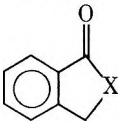
Scheme II



Several alternate mechanisms can account for these results on the basis of limited extrapolations of well-documented reactions of selenium and sulfur compounds. Scheme III represents a possible route via a seleno-Pummerer rearrangement.[5,12] Scheme IV invokes a selenoxide–selenenate rearrangement analogous to similar rearrangements of sulfoxides in solution,[13] in thermal reactions,[14] and in the mass spectrometer.[15] Corresponding rearrangements have been suggested for reactions of selenoxides in solution,[16] and observed in mass spectrometry.[17]

The absence of aliphatic hydrogens β to the selenoxide, and

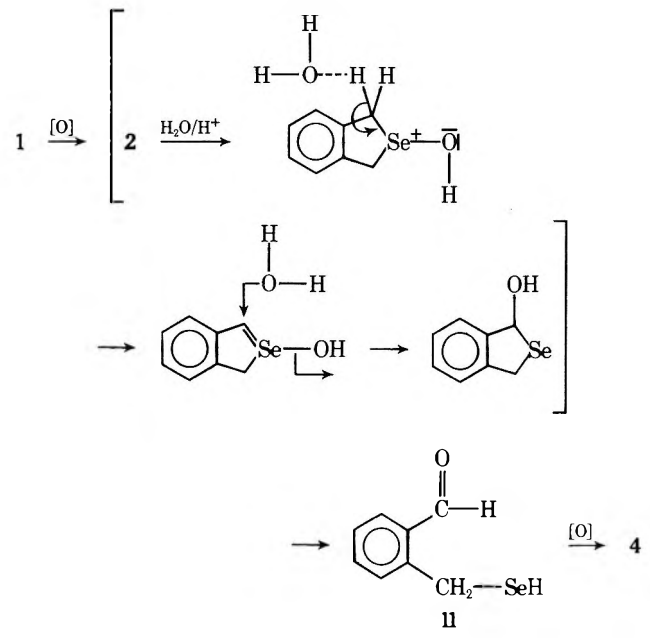
Table I



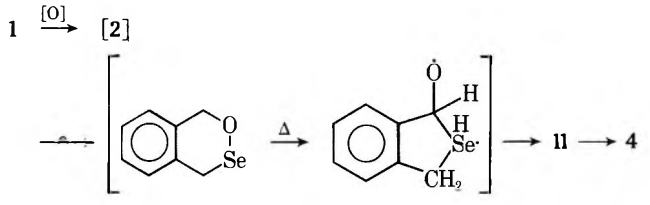
Registry no.	X	δ_{CH_2}	δ_{ArH} (center of multiplet)	δ –C(=O)H	$\nu_{C=O}$, cm^{-1}	Electronegativity of X[a]
87-41-2	O	5.27 (s) [5.32 (s)][c]	7.70 (m) [7.65 (m)][c]	*f*	1761[b]	3.50
1194-57-6	S	4.33	7.45 (m)	*f*	1686[b]	2.44
4938-13-0	Se	4.55 (s)	7.58 (m)	*f*	1668	2.48
	Magdesieva and Vdovin compd	4.28 (s)[d]	7.50 (m)[d]		1695[d]	
	Yellow oil; compd 4	4.28 (s)[e]	7.50 (m)[e]	10.1 (s)[e]	1695[e]	

[a] Reference 9. [b] Reference 10. [c] Reference 11. [d] Reference 3. [e] Measured in same solvents and at same concentrations reported by Magdesieva and Vdovin.[3] [f] No NMR absorption in the region δ 9–11.

Scheme III



Scheme IV



the geometrical restrictions of the phthalide molecules, make unlikely an elimination of the kind so elegantly exploited synthetically by Sharpless,[18] and result in a reactivity apparently unique to this ring system.[5] The similar compound, dibenzyl selenoxide, is stable even when heated to its melting point.[19]

Experimental Section

All temperature readings were uncorrected. IR spectra were determined on a Perkin-Elmer Model 457 spectrophotometer on dilute solutions in KBr pellets. NMR spectra were recorded on a Varian A-60 or HA-100D spectrophotometer in 8% w/w solutions in CCl_4, unless otherwise specified. Mass spectra were determined on a Du Pont 24-491B mass spectrometer. Sodium selenide was purchased from Alfa Inorganics, Inc., Beverly, Mass. Those melting points taken in sealed evacuated capillaries are designated (sec).

2-Selenaindan (1) was prepared from α,α'-dibromo-*o*-xylene (Aldrich Chemical Co.) by the method of Magdesieva and Vdovin.[3] Yields ranged from 34 to 73%, mp 33.5–34.0 °C (sec).

Oxidation of 2-Selenaindan. A stirred solution of 1 (10.0 g, 0.055 mol) in glacial acetic acid (100 ml) at 0–5 °C was treated with a 22% solution of hydrogen peroxide (11.5 ml, 0.08 mol) in the course of 0.5 h. Removal of solvent under reduced pressure at 35 °C followed by steam distillation recovered 1.5 g of unreacted 1. The residual oil was dried azeotropically with benzene to leave 8.3 g of a yellow-orange oil after solvent removal; the oil lightened to a bright yellow on cooling (such thermochromic behavior has previously been noted for diselenides).[20] TLC (Chromar 500, Mallinckrodt, Inc.) with benzene eluent and iodine development gave R_f 1.00 (1), 0.47 (visibly yellow), 0.05 (minor; Se?); in addition, a reddish streak (amorphous Se allotrope) developed on short standing, R_f 0.47–0.23, indicative of decomposition. Column chromatography on a 2-in. diameter column using 400 g of neutral alumina, Brockman activity 1 (Fischer Scientific Co., Inc.) with benzene eluent separated 2.3 g of 1, followed by 3.9 g (58%) of diselenide 4. Column wash with methanol gave 1.6 g of brown tar which displayed no absorptions in the carbonyl region; this material was not further investigated. The upper portion of the column was gray-black at this point, probably owing to precipitated elemental selenium.

Solution of 4 in alcohol and treatment with sodium borohydride completely discharged the yellow coloration, which was re-formed on air oxidation.

Repeat of TLC with the yellow oil, under the same conditions as described above, gave a lone R_f 0.46, with slight streaking of red selenium. After 24 h in the dark, TLC gave a single spot, R_f 0.47, with considerable streaking attributable to selenium. The oil as obtained by column chromatography gave $\nu_{C=O}$ 1695 cm^{-1} in the IR (film between NaCl plates), and the NMR signals noted in the discussion section. The aromatic region of the NMR spectrum of 4 greatly resembles the same region of the NMR spectrum of *o*-tolualdehyde.[21] Attempts to crystallize the oil, with or without a variety of solvents and solvent mixtures, failed. Solvents tried included ether, which reportedly allows recovery of 2-selenophthalide,[3] and alcohols, which notably precipitated amorphous selenium.

Repetitive (three times) preparative TLC (Chromar 1000) of 0.5 g of the oil with benzene eluent gave continuous deposition of red selenium and progressive weight loss of yellow component; a new component appeared near the solvent front which did not develop with iodine (UV visualization: blue) but which had a definite strong odor similar to that of benzaldehyde. A similar odor was observed with a sample left exposed to light for 1 week, or heated on the steam bath for several hours (accompanied by irreversible darkening of the oil).

Preparation of *trans*-o-Methylcinnamic Acid (5). The Doebner condensation product of *o*-tolualdehyde and malonic acid, 5, was synthesized in 90% yield:[22] mp 175–176 °C (lit.[22] mp 176.6–177.2 °C); IR (Nujol) 3000–2800 (broad), 2700–2500 (broad), 1685, 1625 cm^{-1}; NMR (D_2O, NaOD) δ 2.38 (s, 3 H, CH_3), 6.39 (d, 1 H, C=H) (J = 16 Hz), 7.13 (m, 4 H, aromatic), 7.7 (d, 1 H, C=CH) (J = 16 Hz).

Preparation of *trans*-o-Methylethyl Cinnamate (6) The ethyl ester of 17 was prepared via Fischer esterification[23] in 95% yield: bp 114–117 °C (2.2 mm) [lit.[24] bp 148 °C (1.2 mm)]; IR (neat) 2995, 1715, 1638 cm^{-1}; NMR (CCl_4) δ 1.32 (t, 3 H, CH_3), 2.4 (s, 3 H, CH_3), 4.2 (q, 2 H, CH_2), 6.22 (d, 1 H, C=C=H) (J = 16 Hz), 7.22 (m, 4 H, aromatic), 7.85 (d, 1 H, C=C=H) (J = 16 Hz).

Preparation of *trans-o*-(Bromomethyl)ethyl Cinnamate (7). Wohl–Ziegler bromination[25] of **6** yielded **7**. A mixture of **6** (10.0 g, 53 mmol), *N*-bromosuccinimide (9.7 g, 55 mol) (Aldrich), dibenzoyl peroxide (0.8 g), and carbon tetrachloride (200 ml) was heated under reflux until formation of succinimide was complete (3 h). The mixture was cooled and the succinimide filtered and washed with carbon tetrachloride. A preliminary vacuum distillation (short path) afforded two fractions: bp 100–130 °C (0.4 mm) (2.5 g) and bp 130–154 °C (0.4 mm) (10.24 g). The higher boiling fraction was crystallized from methanol (75 ml) at −65 °C to give a 65% yield (9.3 g) of **7**: mp 33.0–33.5 °C; IR (CCl_4) 2995, 1720, 1640 cm^{-1}; NMR (CCl_4) δ 1.31 (t, 3 H, CH_3), 4.22 (q, 2 H, CH_2), 4.5 (s, 2 H, CH_2), 6.30 (d, 1 H, C=CH) (J = 16 Hz), 7.28 (m, 4 H, aromatic), 7.90 (d, 1 H, C=CH) (J = 16 Hz).

Preparation of *o*-Formylbenzyl Bromide (8). A solution of **7** (5.38 g, 20 mmol), methanol (80 ml), and methylene chloride (20 ml) was ozonolyzed at −63 °C. The blue color from the presence of excess ozone indicated that ozonolysis was complete after 0.25 h. After reduction with dimethyl sulfide (10 ml) was complete (0.5 h) (in a preparative reaction, this methanol solution ordinarily was used without further purification), the solution was diluted with benzene (25 ml). The organic phase was washed with water (25 ml) and concentrated to give 1.02 g of clear, yellow liquid. Crude **8** was distilled (bulb to bulb) to give a 10% yield (0.4 g) of brown liquid: bp 70–75 °C (0.4 mm); IR (neat) 2840, 2770, 1700 cm^{-1}; NMR (CCl_4) δ 4.9 (s, 2 H, CH_2), 7.55 (m, 4 H aromatic), 10.1 (s, 1 H, CHO).

Preparation of 2,2-Diformyldibenzyl Diselenide Dimethyl Acetal (10). A solution of **7** (4.0 g, 14.8 mmol) and methanol (100 ml) was ozonolyzed at −60 °C. The blue color from the presence of excess ozone indicates that ozonolysis was complete after 20 min. Reduction with dimethyl sulfide (10 ml) was complete in 0.5 h.

To the stirred reaction mixture, trimethyl orthoformate (28 ml) and *p*-toluenesulfonic acid (0.8 g) were added at room temperature. After stirring for 48 h, the crude product was neutralized with solid potassium carbonate and methanol (80 ml) was distilled off at atmospheric pressure.

The crude acetal in methanol (21 ml) was added dropwise to a freshly prepared solution of bismethoxymagnesium diselenide[26] (50 mmol) at room temperature. After the resulting dark solution was stirred at room temperature for 18 h, water (1 l.) was added to the reaction mixture and the crude product was extracted with diethyl ether (4 × 125 ml). The combined, yellow ether extracts were washed with saturated sodium bicarbonate solution (75 ml) and saturated sodium chloride solution (75 ml), and dried ($MgSO_4$). Concentration of the filtered ether extracts afforded a 26% yield (0.94 g) of crude **10**, which was applied to a hexane-packed column (17 × 9.3 cm) of basic II alumina (Woelm) and eluted with hexane/benzene (30:70). A 10.8% yield (0.39 g) of **10** was obtained as an oil: IR (neat) 2840, 1200, 1110, 1080, 1060 cm^{-1}; NMR ($CDCl_3$) δ 3.22 (s, 12 H, OCH_3), 4.11 (s, 4 H, CH_2), 5.54 (s, 2 H, CH), 7.34 (m, 8 H, aromatic); mass spectrum *m/e* (rel intensity) 490 (39, M^+), 245 (22), 165 (100), 134 (39), 119 (26), 105 (79).

Preparation of 2,2′-Diformyldibenzyl Diselenide (4). A solution of **10** (40 mg) and deuterium oxide (2 drops) in deuterioacetone (360 mg) was added to an NMR tube. Hydrolysis was effected with trifluorodeuterioacetic acid (1 drop) after approximately 2 h at room temperature (a brown, uncharacterized sediment which settled out of the tube at this time was removed from the reaction mixture). The resultant solution was used directly for determining the NMR spectrum. This solution was then concentrated, diluted with anhydrous diethyl ether (2 ml), and dryed over $MgSO_4$. The filtered ether solution crystallized in the freezer and yielded yellow-tan crystals, mp 50–64 °C. Two recrystallizations from anhydrous diethyl ether afforded yellow-tan crystals of **4**: mp 72.5–73.5 °C; IR (neat) 2750, 1695 cm^{-1}; NMR ($CLCl_3$) δ 4.30 (s, 4 H, CH_2), 7.50 (m, 8 H, aromatic), 10.1 (s, 2 H, CHO); mass spectrum *m/e* (rel intensity) 398 (6, M^+), 199 (0.3), 119 (100), 91 (42), 65 (6) (mp of Magdasieva and Vdovin product,[3] 71–72 °C).

2-Selenaphthalide was synthesized from phthalide (Aldrich Chemical Co.) by the method of Gunther.[4b] Samples recrystallized from petroleum ether were used for IR and NMR spectral determinations.

2-Thiaphthalide was synthesized from phthalide (Aldrich Chemical Co.) by the method of Prey.[10] Samples purified by benzene elution from alumina columns gave mp 55.5–56.5 °C (reported 55–60 and 60 °C).[27]

Registry No.—**1**, 35951-68-9; **2**, 58534-05-7; **4**, 60633-89-8; **5**, 939-57-1; **6**, 24393-48-4; **7**, 60633-90-1; **8**, 60633-91-2; **10**, 60633-92-3.

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Homogeneous Catalytic Cyclization and Oxidation of Diols

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The 1,4-diketone unit is an important synthon for a variety of synthetic quests. Such diones are difficult to prepare directly via oxidation of 1,4-diols because other products are actually favored.[2] Hence, several indirect approaches have been developed.[3] These routes are stoichiometric and often involve several steps. We sought an alternative procedure, one that would be catalytic; palladium chloride oxidation of diols was chosen because Pd(II) is a mild oxidizing agent that can be made catalytic in an oxygen environment by the addition of copper chloride. Also, unlike many other oxidizing agents, palladium is not known to effect cleavage of the carbon skeleton in 1,2-diols, so it was considered that Pd(II) might be useful for preparing a variety of diones of differing structural relationships.

The oxidation of simple alcohols with palladium salts has been reported by Lloyd.[4] He found that primary and secon-

Table I. Reactions of Diols with Palladium Catalysts

Registry no.	Entry	Diol	Catalyst	Temp, °C	Time, h	Conversion, %	Ether (%)[a]	Other (%)
513-85-9	1	2,3-Butanediol	*b*	150	24	12		2,3-Butanedione (8) (431-03-8)[f]
1460-57-7	2	*trans*-1,2-Cyclohexanediol	*c*	200	96	Trace		
107-88-0	3	1,3-Butanediol	*c*	150	30	15		2-Butenal (5) (4170-30-3)[f]
110-63-4	4	1,4-Butanediol	*b*	125	24	42	Tetrahydrofuran (40) (109-99-9)[f]	Trace oxidation
	5		*c*	150	6	97	Tetrahydrofuran (95)	
2935-44-6	6	2,5-Hexanediol	*b*	100	24	52	2,5-Dimethyltetrahydrofuran (35) (2144-41-4 (cis))[f]	2,5-Hexanedione (15) (110-13-4)[f]
	7		*c*	150	6	97	2,5-Dimethyltetrahydrofuran (82–92) (2390-94-5 (trans))[f]	
	8		*d*	150	6	40	2,5-Dimethyltetrahydrofuran (39)	
	9		*e*	150	6	85	2,5-Dimethyltetrahydrofuran (80)	
110-03-2	10	2,5-Dimethyl-2,5-hexanediol	*b*	150	6	90	2,2,5,5-Tetramethyldihydrofuran (70) (15045-43-9)[f]	Unidentified
931-71-5 (cis) 6995-79-5 (trans)	11	1,4-Cyclohexanediol (cis and trans)	*c*	150	24	15		See text
111-29-5	12	1,5-Pentanediol	*b*	150	6	100	Tetrahydropyran (75–80) (142-68-7)[f]	Unidentified polymer
	13		*c*	150	6	68	Tetrahydropyran (58)	Unidentified polymer
629-11-8	14	1,6-Hexanediol	*b*	150	24	63	Oxacycloheptane (10) (592-90-5)[f]	1,7-Dioxacyclotetradecane (48) (1080-24-6)[f]
	15		*c*	150	24	56	Oxacycloheptane (8)	1,7-Dioxacyclotetradecane (35)

[a] Yields are based on millimoles of starting diol even when the conversion was <100%. [b] 0.047 M in $PdCl_2$ and 0.063 M in $CuCl_2$. [c] 0.047 M in $PdCl_2$, 0.063 M in $CuCl_2$, and 0.09 M in $Cu(NO_3)_2$. [d] 0.047 M in $PdCl_2$ and 0.09 M in $Cu(NO_3)_2$. [e] 0.047 M in $PdCl_2$ and 0.13 M in NaCl. [f] Registry no.

dary alcohols are oxidized to the corresponding acetals and ketones using mild conditions, typically 70–120 °C. Tertiary alcohols were found to be unreactive. Oxidation of ethylene glycol produced low yields of the cyclic acetal of its glycolic aldehyde, 2-methylol-1,3-dioxolane. Oxidation of 1,4-butanediol eventuated in low yields of γ-butyrolactone and 2-(ω-hydroxybutoxy)tetrahydrofuran.

Because we wished to avoid lactone formation, our study began with a secondary diol, 2,5-hexanediol. Upon heating the diol to 90 °C with a $PdCl_2$–$CuCl_2$–$Cu(NO_3)_2$–O_2 catalyst system, oxidation was observed to be very slow; only by raising the temperature to 130 °C, whereupon a brown gas was evolved, was a fairly rapid reaction rate observed. After the reaction was completed, instead of finding oxidation to be the primary process, it was discovered that cyclization of the diol had occurred to form 2,5-dimethyltetrahydrofuran (a mixture of cis and trans isomers) in very high yield. In view of the mildness of this conversion and its specificity our attention shifted to the ether-forming process. To determine the generality of this observation, a variety of diols were subjected to similar "oxidative" conditions. The products reported in Table I were obtained by distillation and identified by IR, ^1H NMR, and mass spectroscopy.

From the data in Table I it is evident that 1,2- and 1,3-diols react very slowly. *trans*-1,2-Cyclohexanediol was virtually inert to oxidation, even at 200 °C. 2,3-Butanediol was oxidized to its dione in low conversion; other unidentified products were also formed, though in lesser amounts. A great variety of unidentified products were formed from 1,3-butanediol. Carbonyl formation was apparent; 1,2-dihydration was also evidenced as olefins were detected. Other products appeared to be derived from diol–olefin and diol–carbonyl condensations.[5] With the exception of 1,4-cyclohexanediol, 1,4-diols were found to undergo facile reaction and form ethers in high yields. Examples in Table I demonstrate that primary, secondary, and tertiary alcohols all form ethereal products. Cyclization of 1,5-pentanediol occurs readily to generate tetrahydropyran in excellent yield. 1,6-Hexanediol reacts more slowly than 1,4- or 1,5-diols and produces the seven-membered cyclic ether in low yield; actually the 14-membered cyclic diether is the major product. Linear ethers, lactones, or acetals were not detected, though they may have been too nonvolatile to isolate via distillation. Pot residues showed absorptions from 1730 to 1700 cm^{-1}, indicating oxidation. Yields of these residue products are low.

Upon treatment with the palladium "oxidative" catalyst, 1,4-cyclohexanediol (a mixture of cis and trans isomers) conceivably could have produced 1,4-cyclohexanedione and/or 7-oxabicyclo[2.2.1]heptane; instead, after 24 h and a 15% conversion, the only products isolated were high boiling (160–220 °C, 1 mm) and appeared (IR and NMR) to be monoones, acetals, and hemiacetals. Formation of the bicyclic ether apparently was precluded by ring strain.

Concerning these results, several observations are noteworthy. (1) The trend in the ease of cyclization is consistent with that noted for several other reactions in which the ease of ring formation follows the order $4 < 5 \sim 6 > 7$.[6] (2) For 1,4-, 1,5-, and 1,6-diols oxidation is a very minor process at 150 °C.

At lower temperatures (entries 4 and 6) oxidation of a 1,4-diol becomes significant, and modest yields of dione are obtained. However, considering the extended reaction time required to effect a minor conversion, this approach is not considered to be synthetically useful; the only reasonably attractive feature is that this route is catalytic. (3) The reaction is sensitive to the identity of the anion: the rate of cyclization is slower in the presence of nitrate and chloride than chloride alone. Lloyd observed a faster rate of oxidation in the presence of both nitrate and chloride.[4] This difference indicates that the palladium–diol complex undergoing dehydration (cyclization) has more chloride ligands than does the favored palladium–alcohol complex eventuating in carbonyl formation. (4) If copper is omitted (entry 9) the palladium precipitates out after a few minutes. Cyclization continues albeit at a slower rate; heterogeneous catalytic cyclization is well documented for palladium–aluminum alloys, though these are generally employed at significantly higher temperatures.[7] (5) 1,2-Dehydration was observed only with 1,3-butanediol and was slow. Pincol rearrangement products were not observed for any 1,2-diol. (6) The role of Pd(II) in the cyclization is considered to be simply that of a Lewis acid.

Experimental Section

Reactions under Oxygen. Oxidations were carried out in a standard, low-pressure catalytic apparatus (Parr Instrument Co., Model 3911). In typical run a 500-ml glass reactor vessel was charged with 30.0 g of diol along with the desired amounts of catalyst, and the system was sealed, purged three times with oxygen, then pressurized to 60 psig oxygen pressure and rapidly brought to the desired temperature by means of a heating mantle. The temperature was established by standardizing the mantle and variac without pressurizing the system. After the desired time had passed, the reactor was cooled and the contents were collected for analysis.

Product separations and yields were determined by distillation and/or gas chromatography. Product identities were determined by IR, NMR, and mass spectral data.

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A Novel Reaction of Some Fluorospiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ols in 97% Formic Acid

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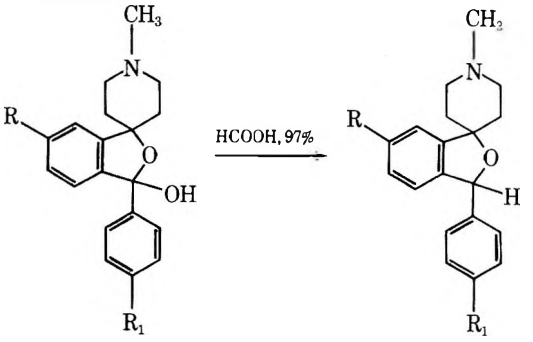
The continued interest in these laboratories in spiro[isobenzofuran-1(3*H*),4′-piperidines] as potential CNS agents[1] prompted an investigation of the recently published[2] reduction in 97% formic acid of 1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (**1a**) to 1′-methyl-3-phen-

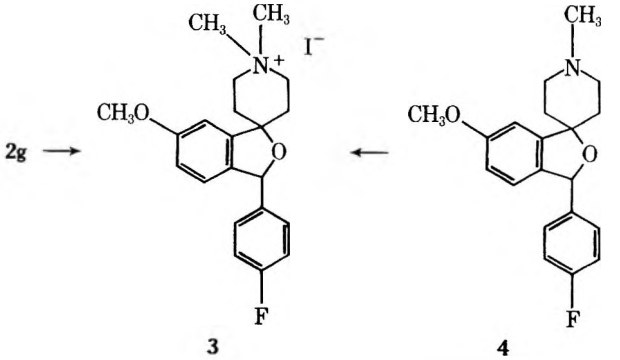


1a, R = R′ = H
b, R = H; R′ = F
c, R = F; R′ = H
d, R = R′ = F

2a, R = R′ = H
b, R = H; R′ = F
c, R = H; R′ = OH
d, R = F; R′ = H
e, R = OH; R′ = H
f, R = R′ = F
g, R = OH; R′ = F

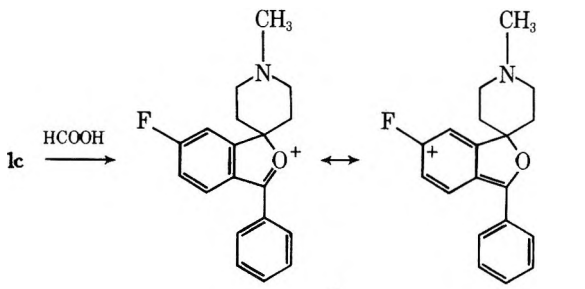
ylspiro[isobenzofuran-1(3*H*),4′-piperidine] (**2a**). We have duplicated the published[2] yield of **2a** using identical procedures. Furthermore, we have found that the 6-chloro- and 3-(4-chlorophenyl) analogues of **1a** are reduced cleanly under these conditions to the corresponding analogues of **2a** in recrystallized yields of 85 and 82%, respectively. TLC and NMR showed no evidence of anomalous by-products in either case. However, the reduction of the 3-(4-fluorophenyl) analogue (**1b**)[2] or the 6-fluoro analogue (**1c**) led not only to the corresponding fluorospiro[isobenzofuran-1(3*H*),4′-piperidines] (**2b** and **2d**, in 71 and 36% yields, respectively) but also led to the hydroxy analogues (**2c** and **2e**, in 14 and 41% yields, respectively). Furthermore, both **2f** and **2g** were isolated (in 42 and 23% yields, respectively) from the reduction of the difluoro analogue (**1d**).

The structures of **2b–f** were proved by comparison of melting points and infrared and ^{1}H NMR spectra with samples obtained in alternate unambiguous syntheses.[1] The orientation of the hydroxy and fluoro substituents of **2g** was



demonstrated by conversion to the methoxy methiodide (**3**). This was shown to be identical with the methiodide obtained from **4** that had been prepared unambiguously.[1]

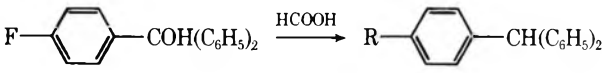
In the case of the reduction of **1c** to **2d** and **2e**, **2d** could not



5

be converted to **2e** by further refluxing in formic acid. This observation suggested that the aromatic fluorine is activated for substitution by the stabilized carbonium ion **5** that is subsequently reduced by formate.[3] The substitution that is observed could result from the capture of water by **5** and the loss of fluoride (or HF). The failure to observe any hydroxylated by-products in the case of the chloro analogues is apparently a manifestation of the greater mobility of fluorine over chlorine in aromatic substitution reactions, particularly in a polar, protic solvent such as formic acid.[4]

The possible intermediacy of **5** in the reduction reactions suggested that the reduction of 4-fluorotriphenylmethanol (**6**) in 97% formic acid would be instructive, as the formation of a stable carbonium ion would also be anticipated.[3,5] Bowden and Watkins[6] studied the reactivity of **6** with 98% formic acid by means of evolved carbon dioxide but did not isolate any products. Taft et al.[7] reported the preparation of 4-fluorotriphenylmethane (**7a**) by the formic acid–sodium formate



6 **7a**, R = F
b, R = OH

reduction of **6**; no product other than **7a** was isolated. Our investigation, however, revealed that 4-hydroxytriphenylmethane (**7b**) is formed in 13% yield together with 4-fluorotriphenylmethane (**7a**, 79% yield) in the reduction of **6** with either formic acid alone or formic acid–sodium formate.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. ^{1}H NMR spectra ($CDCl_3$/Me_4Si) were recorded on a JEOLCO C60HL and the ^{13}C NMR spectra were obtained on a JEOLCO JNM-FX 60 operating at 15 MHz in the Fourier transform mode. The carbon shifts indicated for **7a** and **7b**[10] are from a $CDCl_3$ solution and are in parts per million downfield from Me_4Si. Formic acid (97+%) was obtained from the Aldrich Chemical Co. and was used without further purification. 6-Fluoro-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (**8**) and 3-(4-fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (**1b**) were synthesized according to Marxer et al.[2]

6-Fluoro-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (1c). Phenylmagnesium bromide (0.12 mol) was refluxed for 2 h with 0.081 mol of **8**[2] in 425 ml of dry THF. The reaction mixture was chilled and the insoluble bromomagnesium salt was filtered and washed well with dry Et_2O under anhydrous conditions. This salt was hydrolyzed in aqueous NH_4Cl and the product filtered, washed with water, and recrystallized from EtOAc to give 16.2 g (64%) of **1c**, mp 185–187 °C: NMR δ 1.8–3.1 [m, 11 H, piperidine ring H and CH_3 (s at 2.30)], 5.5 (s, broad, 1 H, OH), 7.0–7.8 (m, 6 H, H-4,5,7 and H-3,4,5 of 3-phenyl), 7.9–8.2 (m, 2 H, H-2,6 of 3-phenyl).

Anal. Calcd for $C_{19}H_{20}FNO_2$: C, 72.82; H, 6.43; N, 4.47. Found: C, 72.72; H, 6.44; N, 4.52.

6-Fluoro-3-(4-fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (1d). In a manner identical with the synthesis of **1c**, **8**[2] was reacted with 4-fluorophenylmagnesium bromide to give, after recrystallization from benzene/THF, 77% of **1d**, mp 179–180.5 °C: NMR δ 1.9–2.9 [m, 11 H, piperidine ring H and CH_3 (s at 2.36)], 4.7 (s, broad, 1 H, OH), 7.1–7.6 (m, 5 H, H-4,5,7 and H-3,5 of 3-phenyl), 7.9–8.2 (m, 2 H, H-2,6 of 3-phenyl).

Anal. Calcd for $C_{19}H_{19}F_2NO_2$: C, 68.87; H, 5.78; N, 4.23. Found: C, 69.10; H, 5.89; N, 4.06.

General Procedure for Formic Acid Reduction of Fluorospiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ols. The method employed was similar to that of Marxer et al.,[2] involving a 2-h reflux of the fluorospiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol in 97% formic acid (ca. 2.5 ml/mmol) followed by the concentration of the reaction mixture under reduced pressure. The residue was distributed between $CHCl_3$ and water, the aqueous phase was made basic with 50% NaOH, and the layers were shaken again. The organic phase was then withdrawn, dried ($MgSO_4$), and concentrated under reduced pressure to give a residue that was worked up in the indicated manner.

3-(4-Fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2b) and 3-(4-Hydroxyphenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2c). On a run of 0.123 mol of **1b**,[2] concentration of the chloroform phase gave a crystalline solid that was treated with hot cyclohexane. The solution was filtered while hot, then allowed to cool. The cyclohexane insoluble material was recrystallized from toluene to give 14% of **2c**, while 71% of **2b** crystallized from the cyclohexane. These two compounds were identical by IR, NMR, and TLC with authentic samples that had been synthesized by unambiguous routes.[1] The melting point of **2c** was 272 °C dec (lit.[1] mp 273–276 °C dec) and **2b** had mp 124–125 °C (lit.[1] mp 126–127 °C).

6-Fluoro-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2d) and 6-Hydroxy-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2e). On a run of 0.05 mol of **1c**, treatment of the gummy residue from the chloroform phase with hot hexane gave 41% of **2e** as an insoluble sediment. Thirty-six percent of **2d** crystallized from the hexane. As above, both **2e** and **2d** were spectrally and chromatographically identical with authentic samples and had mp 200–202 °C dec and 123–124 °C, respectively (lit.[1] mp 207–212 and 127–129 °C).

6-Fluoro-3-(4-fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2f) and 3-(4-Fluorophenyl)-6-hydroxy-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2g). On reduction of 0.03 mol of **1d**, treatment of the concentrated reaction residue with chloroform gave a gummy precipitate that dissolved in 10% NaOH. An emulsion developed when this solution was shaken with chloroform, but cleared when the pH was adjusted to ca. 11. The aqueous phase was separated and adjusted to pH 4–5, precipitating a white solid. This was filtered and combined with a little additional material (identical by TLC) that precipitated from the chloroform over ca. 1 h. Recrystallization from EtOAc/hexane gave 23% of **2g**, mp 219–221 °C dec: NMR δ 1.9–3.2 [m, 11 H, piperidine ring H and CH_3 (s at 2.45)], 6.36 (s, 1 H, H-3), 7.0–7.8 (m, 8 H, aromatic H and OH).

Anal. Calcd for $C_{19}H_{20}FNO_2$: C, 72.82; H, 6.43; N, 4.47; F, 6.06. Found: C, 73.00; H, 6.63; N, 4.36; F, 6.01.

Evaporation of the chloroform phase gave 42% of **2f** as a gummy solid which, after recrystallization from cyclohexane, was spectrally and chromatographically identical with an authentic sample and had mp 131–133 °C (lit.[1] mp 134–135 °C).

1′,1′-Dimethyl-3-(4-fluorophenyl)-6-methoxyspiro[isobenzofuran-1(3*H*),4′-piperidinium] Iodide (3). A solution of **2g** (0.2 g, 0.64 mmol) in DMF (5 ml) was treated first with NaH (0.03 g, 1.25 mmol), warmed to 50 °C, and then treated with MeI (0.12 ml, 1.9 mmol). The addition of water (10 ml) precipitated the methiodide, which was recrystallized from *i*-PrOH/MeOH, mp 301 °C dec: NMR (Me_2SO) δ 1.8–3.0 (m, 4 H, H-3′,5′), 3.4–4.9 (m, 10 H, H-2′,6′ and NCH_3's), 3.98 (s, 3 H, OCH_3), 6.42 (s, 1 H, H-3), 7.1–7.8 (m, 7 H, aromatic H).

Anal. Calcd for $C_{21}H_{25}FINO_2$: C, 53.74; H, 5.37; N, 2.99; I, 27.04. Found: C, 53.58; H, 5.39; N, 2.90; I, 26.88.

Treatment of a solution of 3-(4-fluorophenyl)-6-methoxy-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] hydrobromide[1] (**4**, 0.15 g, 0.46 mmol) in DMF (5 ml) with $NaHCO_3$ (0.3 g, 3.6 mmol) and then MeI (0.04 ml, 0.6 mmol) gave an identical product (melting point, NMR) upon workup as above.

Formic Acid Reduction of 4-Fluorotriphenylmethanol (6). A solution of **6** (4.0 g, 0.014 mol) in 50 ml of 97% formic acid was refluxed for 2 h. The reaction mixture was then cooled and extracted with hexane. The formic acid was concentrated under reduced pressure and the residue worked up as in the previous examples. Concentration of the chloroform phase gave 0.46 g (13%) of 4-hydroxytriphenylmethane (**7b**) as an orange solid. One recrystallization from hexane gave material of mp 109–111 °C (lit.[8] mp 109–110 °C): NMR δ 5.0 (s, broad, 1 H, OH), 5.70 (s, 1 H, CH), 6.92–7.08 (AB d, 2 H, J = 11.0 Hz, *p*-hydroxyphenyl H), 7.20–7.36 (AB d, partially obscured, 2 H, J = 11.0 Hz, *p*-hydroxyphenyl H), 7.2–7.7 (m, 10 H, aromatic H).[10]

Concentration of the hexane extracts gave 2.9 g (79%) of slightly yellow 4-fluorotriphenylmethane (**7a**). One recrystallization from methanol gave colorless crystals, mp 62–63 °C (lit.[9] mp 40–42 °C). Because the melting point difference was great, the sample was analyzed and its NMR spectrum recorded: NMR δ 5.50 (s, 1 H, CH), 6.7–7.3 (m, 14 H, aromatic H).[10]

Anal. Calcd for $C_{19}H_{15}F$: C, 87.00; H, 5.76; F, 7.24. Found: C, 86.83; H, 5.86; F, 7.13.

Similar results were obtained when the formic acid contained 0.1 M sodium formate.

Acknowledgment. The author is indebted to Mr. David Clare for the ^1H NMR measurements and to Mr. Marc Agnew for the ^{13}C NMR measurement and interpretation of **7a** and **7b**. Thanks are also due Mrs. Kathleen Huppert for assistance in preparation of this manuscript.

Registry No.—**1b,** 54595-78-7; **1c,** 60582-06-1; **1d,** 60582-07-2; **2b,** 59142-51-7; **2c,** 59143-29-2; **2d,** 60081-30-3; **2e,** 59143-25-8; **2f,** 59142-50-6; **2g,** 60582-08-3; **3,** 60582-09-4; **4,** 60081-31-4; **6,** 427-39-4; **7a,** 437-23-0; **7b,** 791-92-4; **8,** 54595-73-2; phenyl bromide, 108-86-1; 4-fluorophenyl bromide, 460-00-4.

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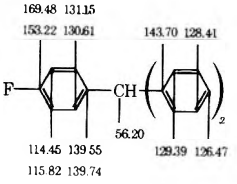
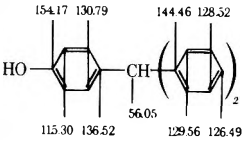
(10) The structures of **7a** and **7b** were confirmed by ^{13}C NMR. The carbon shifts are delineated below.



7a



7b

Enolate Amination with *O*-Mesitylenesulfonylhydroxylamine[1]

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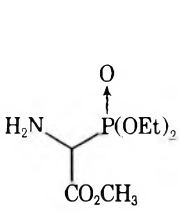
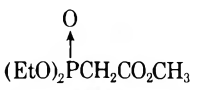
We wish to report the use of enolate amination to achieve a short, simple preparation of a key intermediate for cephalosporin synthesis, methyl α-aminodiethylphosphonoacetate (**1**).[3] Reaction of methyl diethylphosphonoacetate with sodium hydride, followed by the addition of *O*-mesitylenesulfonylhydroxylamine,[4] afforded **1** in 39–47% yield. The major impurity was the neutral **2**, which was conveniently removed by extraction of **1** into aqueous *p*-toluenesulfonic acid. By way of contrast, the previous synthesis of **1** goes in 18–21% yield, and it involves five steps and a chromatography.[3] This method of enolate amination is similar to an approach which has been described by Yamada for the synthesis of α-amino acids.[5]

We have extended the utility of the intermediate **1** to the preparation of a cephem with a methylthio substituent in the



1



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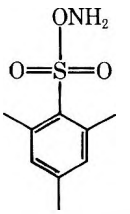

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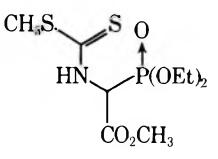

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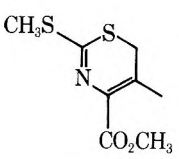

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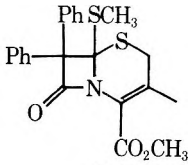

6

6 position. Condensation of **1** with carbon disulfide in aqueous K_2HPO_4, followed by the addition of methyl iodide, gave the dithiocarbamate **4** in 25% yield. By analogy to the Merck report,[6] the reaction of **4** with chloroacetone in acetone containing K_2CO_3 gave the expected thiazine **5** in 81% yield. When a mixture of **5** and diphenylketene was heated under N_2 at 110 °C for a total of 4 h, there was obtained after preparative TLC workup the β-lactam **6**.

We were unsuccessful in our attempts to add azidoketene to the thiazine **5** under conditions which we had used for other imines.[7] The unreactivity of **5** toward azidoketene is consistent with the results from our model studies, and it probably stems in large part from the conjugation of the dithioimine unit with a double bond.

Experimental Section

IR spectra are in $CHCl_3$ and NMR spectra are in $CDCl_3$.

Methyl α-Aminodiethylphosphonoacetate (1). To a suspension of 210 mg of sodium hydride (57% mineral oil dispersion) in 15 ml of dimethoxyethane (DME) was added dropwise 1.07 g (5 mmol) of methyl diethylphosphonoacetate (**2**). After cessation of gas evolution there was added dropwise over a 15-min period a solution of ca. 1.05 g (4.9 mmol) of *O*-mesitylenesulfonylhydroxylamine (**3**)[4,8] (see *Caution*) in 5 ml of DME (temperature held below 30 °C). After stirring for 30 min the mixture was filtered and the filtrate was evaporated in vacuo to give a crude product whose main contaminant was **2**. The crude product was dissolved in $CHCl_3$ and was extracted twice with aqueous *p*-toluenesulfonic acid. The aqueous phase was extracted with $CHCl_3$, basified with K_2HPO_4, and thoroughly extracted with $CHCl_3$. After drying over Na_2SO_4 and removal of solvent there was obtained 530 mg (47%) of TLC pure **1**, whose IR and NMR spectra were in accord with the published values.[3]

Caution: We experienced a mild explosion in attempting to dry 4.5 g of **3** *at room temperature under vacuum.*[8] *Subsequent to this explosion we dispensed with the vacuum drying step of ref 8 and in its place we substituted a routine in which the wet* **3** *obtained according to ref 8 was dissolved in DME and the solution was dried over 4A molecular sieves for ca. 1 h.*

Methyl α-(*S*-Methyldithiocarbonyl)aminodiethylphosphonoacetate (4). A mixture of 225 mg (1 mmol) of **1** 100 mg of carbon disulfide (excess), 87 mg (1 mmol) of dipotassium hydrogen phosphate, and 7 ml of water was stirred at room temperature for 6 h. Methyl iodide (142 mg, 1 mmol) was added and the mixture was stirred for an additional 2 h. The mixture was extracted with an equal volume of diethyl ether. The aqueous layer was treated with 100 mg of carbon disulfide and 40 mg of K_2HPO_4, stirred for 5 h, treated with 142 mg of methyl iodide, stirred for 2 h, and extracted with an equal volume of diethyl ether. The combined ether extract was dried (Na_2SO_4) and concentrated to a gum. A crystalline product, mp 91–92 °C, was obtained from diethyl ether–hexane (80 mg, 25%): IR 1746 cm^{-1}; NMR δ 1.34 (t, J = 7 Hz, CH_2CH_3), 2.64 (s, SCH_3), 3.82 (s, OCH_3), 4.22 (m, $POCH_2CH_3$), 6 (d of d, J_{HP} = 21.5, J_{NH} ~ 7.5 Hz, NHCHP), 7.95 (broad, NH); *m/e* (70 eV) 315 (M^+). Anal. Calcd for $C_9H_{18}NPO_5S_2$: C, 34.28; H, 5.75; N, 4.44. Found: C, 34.41; H, 5.85: N, 4.35.

Synthesis of Methyl 5-Methyl-2-methylthio-6*H*-1,3-thiazine-4-carboxylate (5) and Its Conversion to Methyl 3-Methyl-6-methylthio-7,7-diphenylceph-3-em-4-carboxylate (6). Di-

thiocarbamate 4 (260 mg, 0.825 mmol), chloroacetone (85 mg, 0.92 mmol), potassium carbonate (185 mg, 1.34 mmol), and 25 ml of acetone were stirred at room temperature for 18 h. The solids were filtered and the filtrate was evaporated in vacuo. Chromatography of the residue from ca. 30 g of silica gel gave 145 mg (81%) of TLC pure thiazine **5** as an oil: IR 1720 cm^{-1}; NMR δ 2.24 (s, CH_3C=), 2.53 (s, SCH_3), 3.26 (s, SCH_2), 3.8 (s, OCH_3); *m/e* (70 eV) 217 (M^+). Thiazine **5** (120 mg, 0.55 mmol) and diphenylketene (50 mg, 0.26 mmol) in 5 ml of benzene were evaporated to a thin film in vacuo. This mixture was heated under N_2 in an oil bath at 110 °C for 2 h. TLC showed the presence of a new component. A further quantity of diphenylketene (50 mg in 5 ml of benzene) was added and the mixture was evaporated to a thin film in vacuo. This mixture was heated at 110 °C under N_2 for 2 h. The product was isolated by preparative TLC using benzene. A quantity of 27 mg of the thiazine **5** was recovered. Cephem **6** was a colorless solid: mp 168.5–170 °C dec (25 mg, 14% yield based on consumed thiazine); IR 1772, 1728 cm^{-1}; NMR δ 1.31 (s, SCH_3), 2.08 (s, CH_3C=), 3.09 (d, J_{gem} = 18 Hz, SCH_AH_B), 3.78 (d, J_{gem} = 18 Hz, SCH_AH_B), 3.87 (s, OCH_3), 7.2–7.85 (m, C_6H_5); *m/e* (70 eV) 411 (M^+), 365 ($M - SCH_3$). Anal. Calcd for $C_{22}H_{21}NO_5S_2$: C, 64.21; H, 5.14; N, 3.4. Found: C, 63.9; H, 5.09; N, 3.31.

Registry No.—**1**, 50917-77-6; **2**, 1067-74-9; **3**, 36016-40-7; **4**, 60762-07-4; **5**, 60762-08-5; **6**, 60762-09-6.

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Asymmetric Induction. Enantioselective Alkylation of Cyclohexanone

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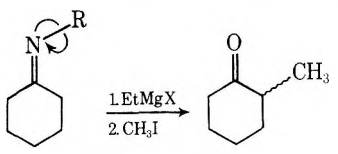
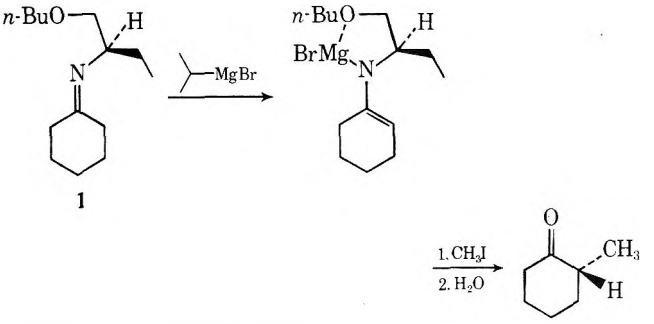
The field of asymmetric induction is one with a plethora of reported efforts but a dearth of actual techniques which lead to a high degree of enantioselectivity in a predictable manner.[1,2] We wish to report a sequence that accomplishes overall the α-alkylation of a ketone, providing a product with a high level of optical purity wherein the absolute configuration can be predicted with some degree of confidence.

The imine anion alkylation sequence of Stork[3] is one of the best techniques for achieving α-alkylation of ketones. The utilization of a chiral amine in forming the imine affords the opportunity for induction of asymmetry in the product, and though this approach has been examined with the cyclohexanone imine derived from isobornylamine, free rotation about the bond indicated would be expected to limit both the



level of and the predictability of the asymmetric induction.[4] We have directly addressed this problem by incorporating into the amine moiety a suitably situated ether oxygen so that *intra*molecular solvation of the metal ion will inhibit rotation. In particular, the *O*-*n*-butyl derivative of (*R*)-2-amino-1-butanol[5] was condensed with cyclohexanone to form the imine **1**. Conversion to the anion with isopropylmagnesium bromide in tetrahydrofuran and then alkylation at −78 °C with methyl



iodide led to (*R*)-2-methylcyclohexanone[6] with an optical purity of 81%. By effecting alkylation at −100 °C, the observed optical purity was increased to 85% while alkylation at reflux afforded the same sense of induction but with an optical purity of only 20%.

Experimental Section

(*R*)-2-Amino-1-butanol. This amine, as supplied by Aldrich Chemical Co. with $\alpha^{28}D$ −6.47° (neat, *l* = 1), was further resolved according to the known procedure.[5] One crystallization as the (+)-tartaric acid salt provided recovered amine with $\alpha^{20}D$ −9.38° (neat, *l* = 1) (lit.[5] max $\alpha^{20}D$ 10.1°, optical purity of 93%).

(*R*)-2-Aminobutyl *n*-Butyl Ether. A solution of 21 g (0.50 mol) of 57% sodium hydride in mineral oil in 200 ml of dimethyl sulfoxide was heated at 80 °C with mechanical stirring under an inert atmosphere for 1 h. To this warm solution was added 42.5 g (0.48 mol) of (*R*)-2-amino-1-butanol as purified above, the heating bath was removed, and the solution was cooled to room temperature, with stirring. After 1 h, the solution was cooled in an ice–water bath and 55 ml (0.51 mol) of *n*-butyl bromide was added over 20 min with vigorous stirring. The reaction mixture was stirred with cooling for an additional 1 h and then the semisolid mixture was washed out into a total volume of 1 l. of water. This solution was extracted with four 200-ml portions of ether, the combined organic layers were extracted with 400 ml of 2.0 N aqueous hydrochloric acid, and the aqueous layer was adjusted to pH 10 with solid potassium hydroxide and then extracted with two 200-ml portions of ether. These organic layers were combined, washed with saturated brine, dried with molecular sieves, concentrated, and then distilled in vacuo, affording 20.6 g (31%) of product, bp 102–106 °C (55 mmHg), $\alpha^{28}D$ −8.37° (neat, *l* = 1).

(*R*)-2-Methylcyclohexanone. The imine **1** was prepared by refluxing a solution of 20 mmol each of cyclohexanone and the amine above in benzene under an inert atmosphere for 12 h with azeotropic removal of water. The benzene was removed in vacuo and a solution of **1** in 5 ml of dry tetrahydrofuran was added under an inert atmosphere to a refluxing solution of 22 mmol of isopropylmagnesium bromide in 15 ml of the same solvent. After 2 h at reflux, the solution was cooled with a dry ice–acetone bath, and 27 mmol of methyl iodide was added dropwise over 15 min with vigorous stirring. The color changed from light yellow to off-white soon after the addition was complete. The reaction was held at −78 °C for a further 15 min, then warmed slowly to 0 °C at which point 11 ml of 2.0 N aqueous hydrochloric acid was added with vigorous stirring. After 15 min the mixture was diluted with 25 ml of pentane, and the organic layer was washed with dilute aqueous oxalic acid, 1 N sodium bicarbonate solution, then with two 20-ml portions of saturated brine. The organic layer was dried with molecular sieves, the solvents removed by distillation, and the residue distilled in vacuo, providing 1.17 g of material with $\alpha^{20}D$ −12.19° (neat, *l* = 1), consisting of 2-methylcycloxanone containing 3% of cyclohexanone (VPC, SE-30 column). After correction for both the presence of recovered cyclohexanone and the optical purity of the amine (93%), and using a maximum rotation[4,6] for 2-methylcyclohexanone of 16.75°, the optical purity was calculated as 81%.

Acknowledgment is gratefully made to the Research Corporation for financial support of this research.

Registry No.—**1**, 60662-02-4; (*R*)-2-amino-1-butanol, 5856-63-3; (*R*)-2-aminobutyl butyl ether, 60662-03-5; butyl bromide, 109-65-9; (*R*)-2-methylcyclohexanone, 22554-29-6; methyl iodide, 74-88-4; cyclohexanone, 108-94-1.

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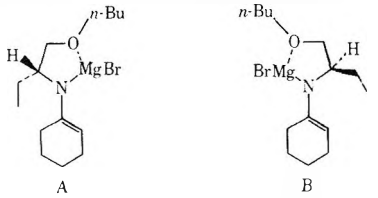

A B

alkylation of proline derived enamines which yield, at best, 43% enantiomeric excess of alkylcyclohexanone.[8] In the present case, however, the magnesium atom would be expected to be aggregated *and/or* highly solvated, thus providing a possibly serious steric inhibition to alkylation via conformation A that would not be apparent in the proline derived enamines. A high degree of enantioselectivity would thus be expected if alkylation occurs mainly or exclusively via B, where the ethyl substitutent is well situated to direct alkylation to the side of the molecule corresponding to the *R* configuration actually obtained.
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Stereoisomerism of Cyproheptadine *N*-Oxide

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The synthesis of cyproheptadine *N*-oxide (**1**) has been described in the patent literature.[1] Subsequent studies of the metabolic fate[2] of cyproheptadine necessitated the resynthesis of **1**. The findings that the hydrogen peroxide oxidation of cyproheptadine provided two isomeric *N*-oxides in the approximate ratio of 75α:25β, and that the α isomer was a major metabolite in the dog, prompted us to investigate the stereochemistry of these isomers.

The isomers were distinguishable by TLC and separable by column chromatography. Their interconversion was evidenced by the precipitation of the β isomer from a refluxing toluene solution of the α isomer. They showed clear differences in their ^{1}H NMR spectra, markedly so in the position of the N-CH_3 singlet which appeared for the β isomer at 0.16 ppm downfield from that of the α isomer (Table I). This distinction was useful for determination of the isomeric purity of the two compounds. The piperidine ring methylene groups, which showed distinct differences in chemical shift in the two isomers, were of little diagnostic value owing to overlapping signals.

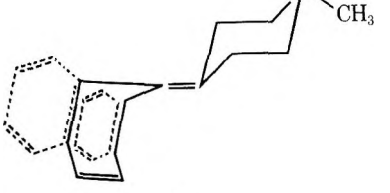
The ^{13}C NMR spectra of the two isomers provided evidence that the N-CH_3 group has the same orientation in both compounds since the chemical shift for the N-CH_3 group appeared at ca. 56 ppm in both isomers. These spectra were determined for the hydrochloride salts of the two isomers. In the ^{13}C NMR spectrum of the quaternary salt, 1,1,4-trimethylpiperidinium iodide, the chemical shift of the equatorial N-CH_3 group is 56.0 ppm and that of the axial N-CH_3 group is 47.8 ppm.[3] Thus, an equatorial N-CH_3 group is suggested for both isomers of the *N*-oxide. This conclusion is supported by a reported[4] ^{1}H NMR study on 1-methylpiperidine 1-oxide which indicated that this potentially mobile *N*-oxide exists preferentially as the conformer with the N^+–O^- bond axial. Other work also has provided evidence that an axial orientation for N-oxidations is preferred.[3,5]

Table I. NMR Assignments of Cyproheptadine *N*-Oxides

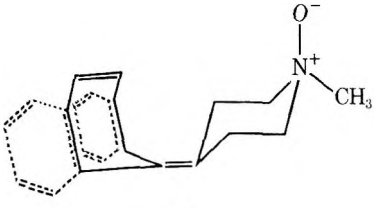
Isomer	δ_{1H} (N-CH_3)[a]	δ_{1H} (C_{10} + C_{11})[a]	δ_{13C} (N-CH_3)[b]
α	3.12	6.88	56.2
β	3.28	6.88	56.0
α + LSR[c]		6.96[d]	
		7.02[e]	
β + LSR[c]		6.84[f]	
		6.78[g]	

[a] Determined for the base in $CDCl_3$, Me_4Si internal standard. [b] Determined for the hydrochloride salt in Me_2SO-d_6, Me_4Si internal standard. [c] LSR = Eu(hfbc)$_3$. [d] 4 mg of LSR added to 5 mg of base/0.5 ml of $CDCl_3$. [e] 8 mg of LSR added to 5 mg of base/0.5 ml of $CDCl_3$. [f] 4 mg of LSR added to 4.6 mg of base/0.5 ml of $CDCl_3$. [g] 6.7 mg of LSR added to 4.6 mg of base/0.5 ml of $CDCl_3$.

Construction of Dreiding models of the cyproheptadine *N*-oxides in conjunction with these data indicated that the two compounds in hand were the isomers **1a** and **1b**, differing only



1a



1b

in the conformation of the dibenzocycloheptene ring. However, the observed spectral characteristics did not permit stereochemical assignments to be made. Further ^{1}H NMR studies employing a lanthanide shift reagent (LSR) provided a basis for assigning the stereochemical relationship between the N^+–O^- bond and the aromatic ring system in the two *N*-oxides. A difference in the location of the C_{10} and C_{11} protons relative to the lanthanide–oxygen–nitrogen grouping is indicated by the fact that these protons in the two isomers are displaced in opposite directions upon addition of the LSR (Table I). The upfield shift of the C_{10} and C_{11} protons in the β isomer implies that these protons are syn with respect to the N^+–O^- bond. This relationship follows from the $3\cos^2\theta - 1$ term of the McConnell–Robertson equation[6] which governs the direction in which a nearby proton is displaced. The angle θ is defined by the donor atom, the lanthanide, and the proton under consideration. The expression changes sign at ca. 50°

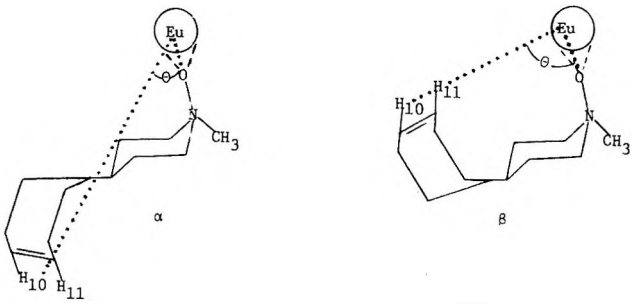


Figure 1. Stereochemical relationship between the N^+–O^- bond and the ethylene bridge protons in the europium complexed $\alpha + \beta$ isomers of cyproheptadine *N*-oxide.

so that a proton associated with a θ value greater than 50°, e.g., the β-C_{10} proton, would experience an upfield shift. These stereochemical relationships then may be represented diagrammatically for the two isomers as in Figure 1 and the α isomer assigned structure **1a**, the β isomer, structure **1b**.

Confirmation of these assignments was sought from calculations of the theoretical values for the $3(\cos^2\theta - 1)/r^3$ term for varied conformations of the isomeric europium complexes.[7] Because of the observed equivalence of H-10 and H-11, the europium atom must be positioned either (a) in a single conformation which is symmetrical with respect to the C_{10}–C_{11} double bond or (b) in two or more rapidly interconverting conformations such that on the average H-10 and H-11 are equivalent. For situation a, only two Eu–O–N–CH_3 dihedral angles, 0 and 180°, are acceptable. The calculations indicated that as long as the Eu–O–N angle was greater than 150°, the predicted direction for the lanthanide-induced shifts was as observed experimentally. In fact, owing to steric hindrance, no Eu–O–N dihedral angle of less than 150° would be expected. For situation b, the two most reasonable conformations are the staggered ones with Eu–O–N–CH_3 dihedral angles of 60 and 300°. In this case, the calculations indicated that the predicted direction of the shifts matched the experimental observations, provided the Eu–O–N angle exceeded 120°. Here also, no smaller Eu–O–N angle would be expected on either electronic or steric grounds.

Thus, the stereochemical relationships for the complexed isomers represented in Figure 1 appear valid and structure **1a** may be assigned to the α isomer and **1b** to the β isomer of cyproheptadine *N*-oxide.

Experimental Section[8]

4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine 1-Oxide (1a and 1b). A stirred solution of cyproheptadine (14.8 g, 0.0515 mol) in 150 ml of MeOH was treated portionwise with 30% H_2O_2 (18 g) and then held at room temperature for about 10 days. The cooled solution was stirred with a suspension of ca. 200 mg of 5% Pt/C in 1 ml of H_2O until the excess peroxide was destroyed. Evaporation of the filtered solution at 35 °C left a solid residue that was dried overnight at 20 mm over P_2O_5. The solid then was pulverized and dried at 0.2 mm over P_2O_5 for 24 h; yield, 15 g of the mixture of isomers.

A 10-g sample of the product was chromatographed on 700 g of SiO_2, eluting with 15 MeOH–85 $CHCl_3$. Fractions containing a single component of R_f 0.5 by TLC (20 MeOH–80 $CHCl_3$ development) were combined to afford the solvated crystalline α base **1a**. This was recrystallized from H_2O to give 5.2 g of the crystalline hemihydrate, mp 188–191 °C, after prolonged drying at room temperature at 0.2 mm.

The α-hydrochloride hemihydrate precipitated from a solution of the base in EtOH–HCl(g) and was recrystallized from EtOH, mp 205–211 °C dec.

Chromatographic fractions containing a single component of R_f 0.4 by TLC were combined to afford the crystalline β base **1b**, mp 194–199 °C dec. This base was not readily recrystallized and was converted to the hydrochloride salt with EtOH–HCl(g). The salt was recrystallized from EtOH to give 1.9 g, mp 223–228 °C dec, after prolonged drying at room temperature at 0.1 mm.

Isomeric purity of the hydrochloride salts was determined to be >95% by both NMR and TLC (10 benzene–80 dioxane–10 concentrated NH_4OH development).

A solution of the α base **1a** (6.0 g, 0.02 mol) in 175 ml of toluene was stirred at reflux for 24 h. After 2 h, a white solid had begun to precipitate. The solid was collected from the cooled mixture by filtration and triturated with hot toluene (50 ml). The remaining solid (4.3 g) was dissolved in EtOH–HCl(g). The hydrochloride salt precipitated and was recrystallized from EtOH to give 4.1 g, mp 228–231 °C dec. This material was identical in all respects with the hydrochloride of the β isomer **1b**.

Acknowledgment. The authors wish to thank Dr. Laurance D. Hall of the University of British Columbia, Vancouver, Canada, for valuable advice and discussion, as well as for the calculations of the configurations of the lanthanide complexes.

Registry No.—**1a**, 54381-42-9; **1a** HCl, 60304-94-1; **1b**, 60251-34-5; **1b** HCl, 60268-34-0; cyproheptadine, 129-03-3.

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(7) These calculations were carried out by Victoria C. Gibb, using a computer program developed in the laboratory of Dr. Laurance D. Hall at the University of British Columbia, Vancouver, Canada. Standard values for all bond lengths and angles were used. Values for $\theta_{O,Eu,H}$ and $r_{Eu,H}$ were measured from Dreiding models, assuming no rotation of the europium atom around the N–O bond and the same relative position and binding constant of the metal for both isomers. Variations in the isomeric binding constants would effect only the magnitude but not the direction of the induced shifts.
(8) Melting points were determined with a calibrated thermometer in a Thomas-Hoover apparatus. ^1H NMR spectra were recorded on a Varian HA-100D spectrometer; ^{13}C NMR on a Varian CFT-20. Thin layer chromatography was done on precoated silica gel plates with UV indicator supplied by Analtech, Inc. Evaporations were carried out in a rotary evaporator at reduced pressure. Satisfactory analytical data (±0.4% for C, H, N) for **1a** and **1b** were submitted for review.

A Convenient Synthesis of Diaryl Methylphosphonates and Transesterification Products Therefrom

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Diaryl methylphosphonates have been useful as both enzyme model substrates[1] and reactive intermediates.[2] The literature describes two basic routes for their preparation. One involves the condensation of methylphosphonic dichloride with the appropriately substituted phenol.[3] However, methylphosphonic dichloride is not readily available and low yields have been reported in some of the aryl ester syntheses using this reagent. The second procedure[4] consists of reacting a triaryl phosphite with 1 equiv of methyl iodide. This Michaelis–Arbuzov rearrangement gives only modest yields, for instance, less than 70% in the case of 1. Moreover, it requires methyl iodide, an expensive reagent. We report, herein, an improved version of the latter rearrangement.

Our procedure involves addition of 1 molar equiv of methanol containing a catalytic amount of methyl iodide to a triaryl phosphite at 200–250 °C. The reaction, on a five molar scale,

Table I. Diaryl Methylphosphonates
$(ArO)_2P(O)Me$

Compd	Phenyl substituent	Yield, %	Bp, °C (mm) Obsd	Bp, °C (mm) Lit.	Mp, °C Obsd	Mp, °C Lit.
1	H	92	138 (0.15)	190–195 (11)[a]	35–36	36–37[a]
2	*p*-Me	56	171 (0.20)	220–225 (12)[a]	Viscous liquid	Viscous liquid
3	*m*-Me	53	145–147 (0.15)	200–205 (7)[a]	Viscous liquid	Viscous liquid
4	*p*-Cl	34	157–160 (0.03)	245 (20)[a]	Viscous liquid	Viscous liquid
5	*p*-*t*-Bu	61	174 (0.07)		65–67	
6	*p*-MeO	72	177–179 (0.03)		Viscous liquid	

[a] See ref 4a.

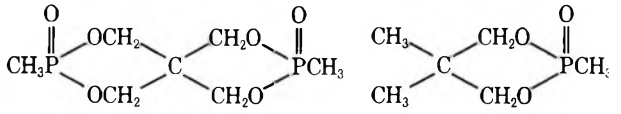
$$(ArO)_3P + MeOH \xrightarrow{0.5\%\ MeI} (ArO)_2P(O)Me + ArOH$$

requires only about 3 h. With triphenyl phosphite, 1 is obtained in 92% yield. The scope of this synthesis is detailed in Table I.

The process can best be rationalized in terms of a two-step mechanism. Initially, methanol transesterifies with the triaryl phosphite to produce diaryl methyl phosphite. Subsequently, this intermediate undergoes rearrangement to the phosphonate with regeneration of the methyl iodide.

Long-chain (C_8 and higher) alcohols have been reported[5] to undergo a similar reaction with triphenyl phosphite. The same report indicated that the lower alcohols would probably require elevated pressure. In our examination of short-chain alcohols under our atmospheric pressure process we noted that ethanol and 2-propanol afforded only diphenyl phosphite. Under these conditions, 1-propanol and 1-butanol transesterified with triphenyl phosphite but the products did not readily rearrange. However, benzyl alcohol did react to form diphenyl benzylphosphonate.

Exemplifying the utility of 1 as a reactive intermediate, various aliphatic alcohols were found capable of displacing phenol from 1. For example, pentaerythritol and neopentyl glycol afforded 8 and 9 in 52 and 33% yields, respectively.



8

9

Experimental Section

NMR spectra were obtained with Varian Associates A-60A (^1H) and Bruker 90 (^{31}P) nuclear magnetic resonance spectrophotometers operating at ambient temperature. Chemical shifts are in parts per million relative to internal Me_4Si (τ units) and external 85% orthophosphoric acid for the ^1H and ^{31}P resonances, respectively. Except where otherwise noted, deuteriochloroform was employed as the NMR solvent. A Hewlett-Packard 5750 instrument was employed for the GLC analysis. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Diphenyl Methylphosphonate (1). A reactor fitted with an efficient condenser, thermometer, mechanical stirrer, and side-arm addition funnel was charged with 1552 g (5.0 mol) of triphenyl phosphite. The reactant was placed under a nitrogen blanket and heated to reflux. A solution of 5.0 g of methyl iodide in 160 g (5.0 mol) of methanol was then slowly added over a 2-h period. Throughout the addition, the temperature of the reactor contents was maintained within the 200–250 °C range. A further 1 h at 215 °C proved sufficient for the reaction to reach completion. Subsequently, an aspirator vacuum distillation removed 468 g (5.0 mol) of phenol containing a small amount of anisole. Thereafter, a high vacuum distillation recovered 1150 g (4.6 mol, 92% yield) of diphenyl methylphosphonate. GLC analysis using a 6-ft column packed with 10% OV-101 on Chromosorb W was employed to monitor the progress of both the reaction and distillation. The ^{31}P signal for compound 1 appeared at −24.0 ppm. ^1H NMR signals were seen at τ 8.36 (3 H, doublet, J = 18 Hz, CH_3P) and 2.9–2.5 (10 H, multiplet, phenyl).

General Procedure. The method as outlined for 1 was that employed for synthesis of the other analogues. Preparation of compounds 2–5 began from PCl_3 and the appropriate phenol. These were run on a 0.5 molar scale. The resultant phosphites were then purged of HCl and further reacted with methanol. Reported yields are based on starting PCl_3.

Bis(*p*-tolyl) Methylphosphonate (2). ^1H NMR signals were observed at τ 8.37 (3 H, doublet, J = 16.5 Hz, CH_3P), 7.77 (6 H, singlet, CH_3Ar), and 2.89 (8 H, broad singlet, phenyl), The ^{31}P NMR signal appeared at −23.6 ppm.

Bis(*m*-tolyl) Methylphosphonate (3). ^1H NMR signals were observed at τ 8.30 (3 H, doublet, J = 17.5 Hz, CH_3P), 7.72 (6 H, singlet, CH_3Ar), and 3.4–2.5 (8 H, multiplet, phenyl). The ^{31}P NMR signal appeared at −23.5 ppm.

Bis(*p*-chlorophenyl) Methylphosphonate (4). ^1H NMR signals were observed at τ 8.24 (3 H, doublet, J = 17.5 Hz, CH_3P) and 3.0–2.3 (8 H, multiplet, phenyl). The ^{31}P NMR signal appeared at −24.8 ppm.

Bis(*p*-*tert*-butylphenyl) Methylphosphonate (5). ^1H NMR signals were observed at τ 8.70 [18 H, singlet, $(CH_3)_3C$], 8.26 (3 H, doublet, J = 17.5 Hz, CH_3P), and 2.75 (8 H, A_2B_2 quartet, phenyl). The ^{31}P NMR signal appeared at −23.9 ppm.

Anal. Calcd for $C_{21}H_{29}O_3P$: C, 70.00; H, 8.06; P, 8.61. Found: C, 69.83; H, 8.21; P, 8.50.

Bis(*p*-methoxyphenyl) Methylphosphonate (6). ^1H NMR signals were observed at τ 8.35)3 H, doublet, J = 17.5 Hz, CH_3P), 6.32 (6 H, singlet, CH_3O), and 3.08 (8 H, A_2B_2 quartet, phenyl). The ^{31}P NMR signal appeared at −24.6 ppm.

Anal. Calcd for $C_{15}H_{17}O_5P$: C, 58.44; H, 5.52; P, 10.10. Found: C, 58.00; H, 5.74; P, 10.10.

Diphenyl Benzylphosphonate (7). To a flask containing 155 g (0.5 mol) of refluxing triphenyl phosphite was added over a 1.5-h period a mixture of 54 g (0.5 mol) of benzyl alcohol and 0.5 g of methyl iodide. The reaction temperature was maintained at 200–250 °C for a further 3.5 h. Thereafter, 43.9 g (0.47 mol) of phenol by-product was removed by distillation. The product (7) distilled at 186–187 °C (0.06 mm) and weighed 113 g (0.35 mol, 70% yield). Upon cooling 7 solidified. Recrystallization in ligroin gave white needles with mp 61–62 °C (lit.[4a] mp 60 °C). ^1H NMR signals (neat) were observed at τ 6.62 (2 H, doublet, J = 22 Hz, CH_2OP) and 3.2–2.6 (15 H, multiplet, phenyl). A ^{31}P NMR signal was observed at −19.5 ppm.

3,9-Dimethyl-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-Dioxide (8). A mixture of 74.4 g (0.30 mol) of diphenyl methylphosphonate, 20.4 g (0.15 mol) of pentaerythritol, and 0.1 g of magnesium chloride was heated together at 192–205 °C for 6 h. Thereafter, 54.6 g (0.58 mol) of phenol was removed under a 26-mm vacuum and a pot temperature of 120–200 °C. Crude product (38.2 g) remained behind in the reactor. Sublimation at 210 °C (0.05 mm) afforded 20.1 g (0.078 mol, 52% yield) of 8. The product was a hygroscopic, white, crystalline solid, mp 240–241 °C (lit.[6] mp 239–241 °C). ^1H NMR signals (Me_2SO-d_6 as solvent) were observed at τ 8.36 (6 H, doublet, J = 17 Hz, CH_3P) and 6.0–5.4 (8 H, multiplet, CH_2O). The ^{31}P NMR signal appeared at −27.2 ppm.

2,5,5-Trimethyl-2-oxo-1,3,2-dioxaphosphorinane (9). A reactor was charged with 74.4 g (0.30 mol) of diphenyl methylphosphonate, 31.2 g (0.30 mol) of dry neopentyl glycol, and 0.2 g of magnesium chloride. These reactants were heated at 210–250 °C for 4 h. Subsequently, phenol (36 g, 0.38 mol) was removed by distillation. Further distillation afforded a liquid with bp 128–130 °C (3.4 mm) that soon solidified. Recrystallization from benzene–heptane afforded white crystals, mp 119–121 °C (lit.[7] mp 119–121 °C), weighing 16.0 g (0.10 mol, 33% yield). The observed ^1H NMR spectrum of 9 was consistent with that reported by Edmundson.[8]

Registry No.—1, 7526-26-3; 2, 60142-74-9; 3, 60142-73-8; 4, 6395-59-1; 5, 60705-72-8; 6, 60705-73-9; 7, 10419-87-1; 8, 3001-98-7;

9, 873-97-2; $(ArO)_3P$ (Ar = p-MeC_6H_4), 620-42-8; $(ArO)_3P$ (Ar = m-MeC_6H_4), 620-38-2; $(ArO)_3P$ (Ar = p-ClC_6H_4), 5679-61-8; $(ArO)_3P$ (Ar = p-t-BuC_6H_4), 4235-89-6; $(ArO)_3P$ (Ar = p-$MeOC_6H_4$), 19909-81-0; $(ArO)_3P$ (Ar = Ph), 101-02-0; methanol, 67-56-1; benzyl alcohol, 100-51-6; pentaerythritol, 115-77-5; neopentyl glycol, 126-30-7; phosphorus trichloride, 7719-12-2; p-methylphenol, 106-44-5; m-methylphenol, 108-39-4; p-chlorophenol, 106-48-9; p-tert-butylphenol, 98-54-4; p-methoxyphenol, 150-76-5; phenol, 108-95-2.

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A Convenient Determination of σ^+ Values

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The empirical σ^+ parameters devised by Brown and Okamoto[1] to account for the effect of substituents in aromatic electrophilic substitution reactions possess a much greater generality. For instance, Streitwieser et al.[2] have recently demonstrated their applicability to gas-phase protonation of benzenes.

We report here an easy and straightforward method for measurement of previously unavailable σ^+ values, from NMR chemical shifts in meta- or para-substituted benzylidene malononitriles[3] $XC_6H_4CH{=}C(CN)_2$. These are prepared according to standard procedures.[4] The singlet resonance for the olefinic proton is readily identified in the ^1H NMR spectrum. Relationship 1

$$\sigma^+ = 3.57\delta_H - 29.6 \qquad \text{(para substituents)} \quad (1)$$

holds for 5% w/v acetone-d_6 solutions,[5] with a correlation coefficient of 0.989 (11 points) (Figure 1). The σ^+ parameters are thus determined to ±0.3 at the 99% confidence level (three standard deviations). Use of the ^{13}C chemical shift for the cyano-bearing carbon, with a distinctive chemical shift of 80 ± 10 ppm,

$$\sigma^+ = 0.16\delta_C - 13.4 \qquad \text{(para substituents)} \quad (2)$$

leads to better accuracy also for deuteriochloroform solutions (25% w/v) with a correlation coefficient of 0.998 (seven points, including the substituents in the recommended[6] basis set) (Figure 2). Equation 2 is both more *sensitive* and more *accurate* than previous correlations between ^{13}C chemical shifts

Table I. Comparison with Published Correlations Between σ^+ and ^{13}C Chemical Shifts

Compd	Slope	Standard deviation	Ref
Triaryl carbocations	−0.06	0.23	7
Benzenes	0.12	0.19	8
Benzylidenemalononitriles	0.16	0.04	This work

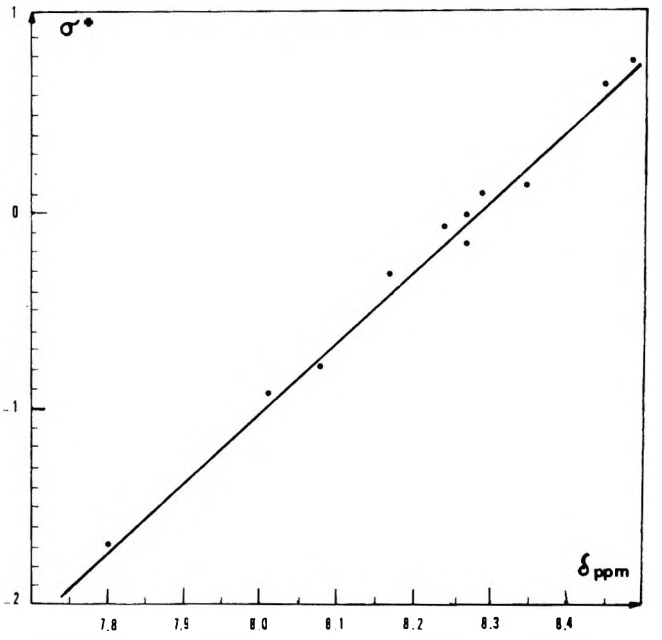

Figure 1. ^1H chemical shift for the olefinic proton vs. σ^+ in acetone-d_6 solution: $\sigma^+ = 3.574\delta - 29.579$.

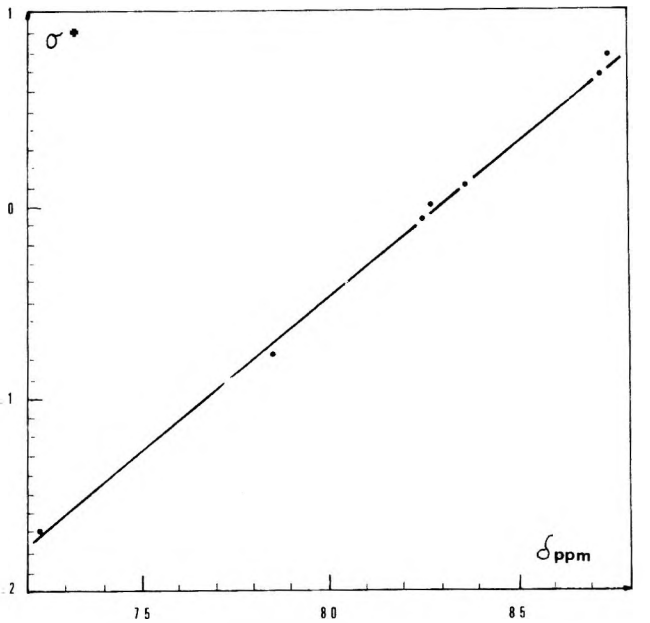

Figure 2. ^{13}C chemical shift for the cyano-bearing cation vs. σ^+ in chloroform-d solution: $\sigma^+ = 0.162\delta - 13.415$

and σ^+ parameters (Table I). Another advantage of our approach is the possibility of evaluating σ^+ for a meta substituent, since in acetone-d_6 solution a *single* relationship holds

$$\sigma^+ = 0.18\delta_C - 14.8 \qquad \text{(meta and para substituents)} \quad (3)$$

with a correlation coefficient of 0.993 (nine points) (Figure 3). This last relationship (3) yields σ^+ values to ±0.08 at the 99% confidence level.

As an application, we have used this method to determine unknown σ^+ values (Table II). Our values of σ^+ for the mesylate and tosylate groups, viz., 0.15 and 0.16, respectively, are of interest since they complement the σ_p, σ_I, and σ^* values just determined, using acidities or ^{19}F chemical shifts, by Stang and Anderson.[9] The σ^+ value for the dicyanomethylidene $HC{=}C(CN)_2$ substituent points to a powerful acceptor, in the same class as the cyano or nitro groups.

In summary, benzylidene malononitriles display strong polarization of the exocyclic double bond putting positive

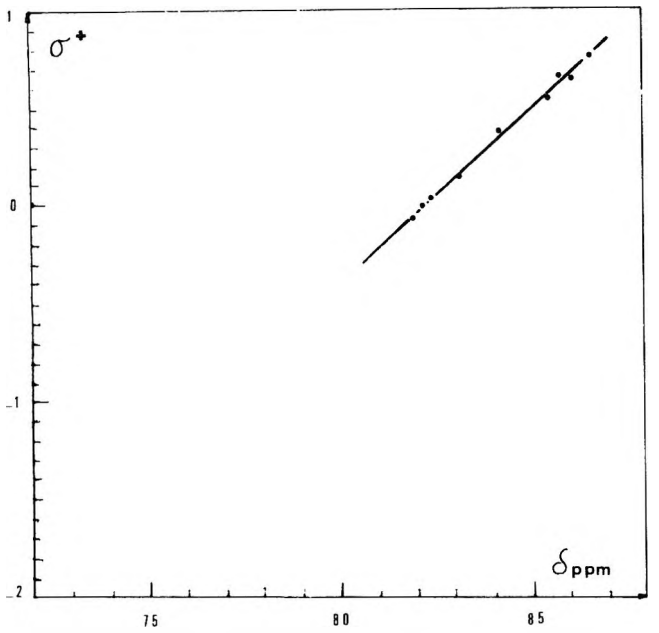

Figure 3. ^{13}C chemical shift for the cyano-bearing cation vs. σ^+ in acetone-d_6 solution: $\sigma^+ = 0.180\delta - 14.812$.

Table II. Sample Values of σ^+ Parameters

Para substituent	Nucleus probe	$\sigma^+(\pm 3\sigma)$
$CH{=}C(CN)_2$	C-4[8]	$0.8^2 \pm 0.5$
$CH{=}C(CN)_2$	olef H	$0.5^5 \pm 0.3$
(acetone-d_6)	δ 8.43	
$OCH_2C_6H_5$	olef H	$-0.6^6 \pm 0.3$
(acetone-d_6)	δ 8.09	
OSO_2CH_3	olef H	$0.1^6 \pm 0.3$
(acetone-d_6)	δ 8.32	
OSO_2CH_3	C-8	$0.1^5 \pm 0.1$
(acetone-d_6)	δ 83.11	
$OSO_2C_6H_4CH_3(p)$	olef H	$-0.0^6 \pm 0.3$
(acetone-d_6)	δ 8.26	
$OSO_2C_6H_4CH_3(p)$	C-8	$0.1^6 \pm 0.1$
(acetone-d_6)	δ 83.18	

charge on the α carbon.[11] The empirical finding that either H-7 or C-8[12] have resonances extremely sensitive to σ^+ values for the meta or para ring substituent affords an easy, if not extremely accurate, determination of this important parameter.

Since this note was submitted for publication, Posner and Hall have reported[13] an analogous method for determination of σ^+. Their results, although differing somewhat in the solvents used and in the substituent investigated, are complementary to ours.

Experimental Section

^1H NMR spectra were obtained on a Varian T-60 spectrometer, using tetramethylsilane as internal reference, whereas ^{13}C NMR spectra were determined on a Bruker HFX-90 spectrometer, field locked on deuterium (chloroform-d or acetone-d_6) and linked to a Nicolet Fourier transform system. The solvent peak (77.5 ppm) was used as reference for chloroform-d solutions, and a trace of internal methylene chloride (54.0 ppm) served as standard for acetone-d_6 solutions.

The substituted benzylidenemalononitriles were prepared from the corresponding substituted benzaldehyde and malononitrile according to the standard procedure of Corson and Stoughton,[4] except for the p-SO_3CH_3 and the p-$SO_3C_6H_4CH_3(p)$ derivatives, which were prepared by reaction between p-hydroxybenzylidenemalononitrile and the corresponding sulfonyl chloride in pyridine solution. All ^1H and ^{13}C NMR spectra were fully compatible with the correct benzylidenemalononitrile structures.

All the compounds were crystallized to constant melting points, in excellent agreement with data in the literature.[3,4] The following values (uncorrected) have not been previously reported (substituent, mp): p-C_6H_5, 142–143 °C; m-CN, 147–148 °C; p-SO_3CH_3, 117.5 °C; p-$SO_3C_6H_4CH_3(p)$, 150.5–151 °C; p-$CH{=}C(CN)_2$, 274.5–275 °C.

^1H Chemical Shift Data for the Olefinic Proton in Acetone-d_6 Solution [substituent, δ (ppm), σ^+]: p-$N(CH_3)_2$, 7.80, −1.70; p-OH, 8.01, −0.92; p-OMe, 8.08, −0.78; p-Me, 8.17, −0.31; p-C_6H_5, 8.27, −0.17; p-F, 8.24, −0.07; p-H, 8.27, 0.00; p-Cl, 8.29, 0.11; p-Br, 8.35, 0.15; p-CN, 8.45, 0.66; p-NO_2, 8.49, 0.79.

^{13}C Chemical Shift for the Cyano-Bearing Carbon in Chloroform-d Solution[14] [substituent, δ (ppm), σ^+]: p-$N(CH_3)_2$, 72.21, −1.70; p-OMe, 78.45, −0.78; p-F, 82.47, −0.07; p-H, 82.67, 0.00; p-Cl, 83.55, 0.11; p-CN, 87.24, 0.66; p-NO_2, 87.47, 0.79.

^{13}C Chemical Shift for the Cyano-Bearing Carbon in Acetone-d_6 Solution[14] [substituent, δ (ppm), σ^+]: p-F, 81.88, −0.07; p-H, 82.21, 0.00; m-OMe, 82.46, 0.05; p-Br, 83.14, 0.15; m-Cl, 84.19, 0.40; m-CN, 85.46, 0.56; p-CN, 86.04, 0.66; m-NO_2, 85.72, 0.67; p-NO_2, 86.61, 0.79.

Acknowledgments. We thank the Fonds de la Recherche Fondamentale Collective for their help in purchasing the Bruker HFX-90 spectrometer used in this study, and Professor Peter Stang (University of Utah) for suggesting application of the method to the mesylate and tosylate groups.

Registry No.—$XC_6H_4CH{=}C(CN)_2$ (X = p-Ph), 26089-09-8; (X = m-CN), 60595-33-7; (X = p-SO_3CH_3), 60595-34-8; (X = p-$SO_3C_6H_4CH_3(p)$), 60595-35-9; (X = p-$H{=}C(CN)_2$), 17239-69-9; (X = p-NMe_2), 2826-28-0; (X = p-OH), 3785-90-8; (X = p-OMe), 2826-26-8; (X = p-Me), 2826-25-7; (X = p-F), 2826-22-4; (X = p-H), 2700-22-3; (X = p-Cl), 1867-38-5; (X = p-Br), 2826-24-6; (X = p-NO_2), 2700-23-4; (X = m-OMe), 2972-72-7; (X = m-Cl), 2972-73-8; (X = p-CN), 36937-92-5; (X = m-NO_2), 2826-32-6.

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An Improved Preparation of Phenolic [1.1.1.1]Metacyclophanes

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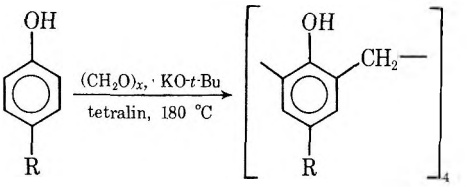
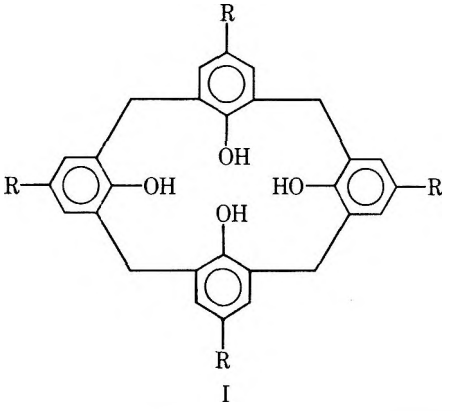
Phenolic [1.1.1.1.]metacyclophanes (I) represent a very interesting and little studied class of compounds. For example, the cuplike structure[1] and strong complexing ability[1,2] of these macrocycles permit these molecules to act as unique models for enzyme–substrate complexes.[3] The macrocyclic structure

Table I



Compd[a]	R	% yield	Mp, °C[b]	Lit. mp, °C	Mol wt	Theor mol wt
1	CH_3	54	370–375	>360[2,6]	480[c]	480
2	$C(CH_3)_3$	53	342–344	330–332[1]	677,[d] 648[e]	696
3	Ph	81	340–350	330–60[2]	741[d]	728
4	OCH_3	92	380–385	*f*	544[c]	544
5	CO_2CH_3	32	380–390	*f*	672[d]	656

[a] All compounds gave satisfactory (C, H) elemental analyses. [b] Decomposition points obtained in sealed capillary tubes. [c] MS. [d] Rast method in camphor. [e] NMR using acetophenone as the internal standard. [f] New compound.



I

has been proven using x-ray analysis,[1] spectroscopy (IR, NMR), and multistep synthesis.[4,5]

Previous preparations of these compounds have been achieved mainly through the two-step method of condensing a para-substituted phenol with formaldehyde and base, and then forming the cyclic tetramer by heating the reaction mixture in linseed oil at 220 °C.[1,2,6] This procedure is cumbersome and furnishes the compounds in low yields.[7]

These phenolic [1.1.1.1]metacyclophanes can now be prepared in good yield (Table I) in a one-flask reaction procedure in which a para-substituted phenol is condensed with formaldehyde (paraformaldehyde) in the presence of potassium *tert*-butoxide. Conducting this reaction in tetralin at 180–200 °C effects both condensation and ring closure; the phenolic [1.1.1.1]metacyclophane precipitates from the reaction mixture in a good state of purity. Although limitations exist, in that, *p*-Cl-, *p*-Br-, and *p*-acetylaminophenols give only amorphous, unworkable materials, this procedure is much more satisfactory than the previously reported two-step sequence.

The phenolic [1.1.1.1]metacyclophane structure was proven through spectroscopic (NMR, IR, MS) and molecular weight determinations, and by comparison with published data for the authentic samples.[1,2]

Experimental Section

Melting points were taken in sealed capillary tubes using a Mel-Temp apparatus and are uncorrected. NMR spectra were obtained in pyridine-d_5 solution on a Varian T60 spectrometer using tetramethylsilane (δ 0.0) as an internal standard. Mass spectra (MS) were obtained at 80 eV on a Varian MAT-111 using a heated direct inlet probe. Infrared spectra (IR) were obtained in KBr on a Perkin-Elmer Model 337 grating spectrometer. Commercial phenols, potassium *tert*-butoxide and tetralin (Aldrich), and paraformaldehyde (Fisher) were used as obtained.

General Procedure. A mixture of para-substituted phenol (0.1 mol), potassium *tert*-butoxide (2–3 g), paraformaldehyde (10 g), and tetralin (200 ml) was placed in a 500-ml round-bottomed flask connected to a Dean-Stark trap and condenser fitted with a drying tube. The mixture was heated slowly to 180–200 °C (thermocouple) for 6–8 h during which the product precipitated as a yellow-white powder. after the mixture had cooled, the powder was collected by suction filtration and washed with isopropyl alcohol. The powder was then dissolved in pyridine and filtered to remove gummy, resinous materials. The phenolic [1.1.1.1]metacyclophane was obtained in pure form on acidification of the pyridine solution with cold dilute hydrochloric acid followed by filtration and drying under vacuum to remove occluded solvent(s).

Spectra, General. The IR spectra of **1–5** all contained strong absorption at 3200–3100 cm^{-1} (broad, OH) and a sharp band at 851–849 cm^{-1} (1,2,4,6 substitution). **5** displayed carbonyl absorption at 1705 cm^{-1}.

The NMR spectra for **1–5** all contained the following absorptions: δ 3.8–4.1 (broad, 2 H, CH_2), 7.0–7.2 (s, 2 H, aromatic), 7.9–8.3 (s, 1 H, OH). The para substituent was observed as a singlet for the correct proton count at δ 4.1 (CH_3), 1.2 [$-C(CH_3)_3$], 7.2 (Ph, m), 3.8 (OCH_3), 3.6 (CO_2CH_3).

The MS of **1** and **5** showed the parent ion as the most intense ion.

Acetone Complex with 2. A mixture of **2** and acetone was allowed to stand until the acetone had completely evaporated and a dry powder complex was obtained. The NMR spectrum of the complex showed acetone at δ 2.0. The complex stoichiometry was obtained from comparison of the integral ratios of acetone (δ 2.0) and the *tert*-butyl peak (δ 1.2) as 1:1.

Acknowledgment. We thank Dr. C. D. Gutsche, Washington University, St. Louis, Mo., for helpful discussions and literature information.

Registry No.—**1**, 53255-02-0; **2**, 60705-62-6; **3**, 60705-63-7; **4**, 60705-64-8; **5**, 60705-65-9; HOC_6H_4-*p*-R (R = CH_3), 106-44-5; HOC_6H_4-*p*-R (R = $C(CH_3)_3$), 98-54-4; HOC_6H_4-*p*-R (R = Ph), 92-69-3; HOC_6H_4-*p*-R (R = OCH_3), 150-76-5; HOC_6H_4-*p*-R (R = CO_2CH_3), 99-76-3.

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(8) Metacyclophane nomenclature:[9] (1) 4,11,18,25-tetramethyl-7,14,21,28-tetrahydroxy[1.1.1.1]metacyclophane; (2) 4,11,18,25-tetra-*tert*-butyl-7,14,21,28-tetrahydroxy[1.1.1.1]metacyclophane; (3) 4,11,18,25-tetraphenyl-7,14,21,28-tetrahydroxy[1.1.1.1]metacyclophane; (4) 4,11,18,-25-tetramethoxy-7,14,21,28-tetrahydroxy[1.1.1.1]metacyclcphane; (5) 4,11,18,25-tetracarbomethoxy-7,14,21,28-tetrahydroxy[1.1.1.1]metacyclophane.
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Nuclear Magnetic Resonance Determination of Enantiomeric Composition and Absolute Configuration of γ-Lactones Using Chiral 2,2,2-Trifluoro-1-(9-anthryl)ethanol

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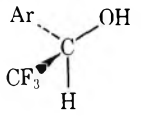
Since lactone functionality is ubiquitous among nature's molecules, the determination of absolute configuration and enantiomeric purity of variously substituted chiral lactones is one that is periodically encountered by those synthesizing or elucidating the structures of natural products. Chiroptic methods are useful for determining absolute configurations of some lactones depending upon the substitution patterns.[1] X-ray structural analysis is valuable (in the case of suitably crystalline materials) but time consuming and hence expensive. In this paper, we describe an NMR method for simultaneously determining absolute configurations and enantiomeric purities of δ-lactones that is, in principle, applicable regardless of substitution pattern.

Chiral aryltrifluoromethylcarbinols, **1**, are known to render the NMR spectra of enantiomers "nonequivalent" for a



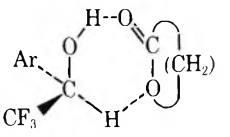
1

1a, Ar = phenyl
b, Ar = α-naphthyl
c, Ar = 9-anthryl

number of solute types. The observation of separate signals for each enantiomer allows determination of enantiomeric purity *without reference to an external standard of enantiomeric purity.*[2] This is done by measurement of the relative intensities of the two sets of signals.

The induced spectral nonequivalence arises from the formation of short-lived diastereomeric solvates that have nonidentical spectra as a consequence of the population of rather specific conformations. Knowledge of the structures of these conformations and the absolute configuration of the carbinol allows assignment of absolute configuration to each of the solute enantiomers on the basis of the sense of nonequivalence[3] induced by chiral **1**. While the phenylcarbinol **1a** or the naphthylcarbinol **1b** have been used most frequently for the NMR determination of enantiomeric purity and absolute configuration, we have found that, for such determinations, the next higher analogue, 2,2,2-trifluoro-1-(9-anthryl)ethanol (**1c**), is superior to either **1a** or **1b** in several ways. Most importantly, **1c** has the ability to induce greater spectral nonequivalence between enantiomeric solutes than either **1a** or **1b** despite its modest solubility compared to **1a** and **1b**. While nonequivalence magnitudes depend upon the solute involved and the experimental conditions utilized, it is not uncommon to observe nonequivalence magnitudes of 0.1 ppm. In addition, fluoro alcohol **1c** is readily prepared and resolved and is conveniently handled. It is not sensitive toward moisture and can be easily recovered after use.

Solvation Models. Experience has shown that one fundamental solvation model accounts for the nonequivalence observed for the enantiomers of a variety of solute types. Both the hydroxyl and carbinyl hydrogen of **1** are capable of bonding interactions with basic sites, the former giving rise to the stronger interaction. A priori, one expects some chelatelike solvation of a lactone by **1** as shown in **2**. The stronger primary hydrogen bond is expected to occur between the hydroxyl of **1** and the carbonyl oxygen of the lactone, in view of the greater basicity of this oxygen compared to the ring oxygen.[5] Subsequent to this primary *intermolecular* interaction, the weaker carbinyl hydrogen bond,[6] being *intramolecular*, can effectively control conformer population so that **2** represents a major solution conformer. Substituents on either face of the lactone respond differently to the shielding effect of the aromatic substituent of **1**. For example, in the generalized drawings **3** and **4**, it will be seen that, in the absence of addi-



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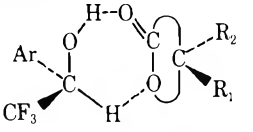

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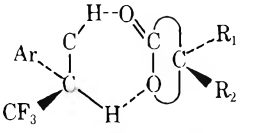

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tional carbinol–lactone interactions, the only difference between the two diastereomeric solvates (to a first approximation) is that R_2 is cis to Ar in **3** but trans in **4**. The converse occurs for R_1. Consequently, the enantiomer incorporated into **3** will have its time averaged R_2 resonance upfield and its R_1 resonance downfield relative to the same signals of the other enantiomer.[7] Possible effects of dissimilar extents of solvation can be minimized through use of a severalfold excess of **1**.

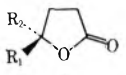
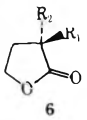
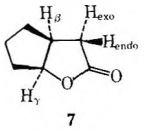
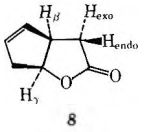
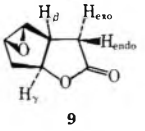
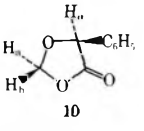
These expectations are born out by the data in Table I. All of the lactones in Table I exhibit nonequivalence for at least one set of enantiomeric protons in the presence of a severalfold excess of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**1c**). Enantiomeric purities could be accurately determined for all lactones except **6b** and **6c**, which exhibit partial overlap of enantiomeric resonances. Enantiomeric purities could, however, be estimated for these lactones.

The ring protons of type **5** and **6** lactones couple extensively and give rise to spectral patterns that complicate the interpretation of the induced nonequivalence. This problem, less severe when substituents simplify the ring pattern (as in **7**, **8**, and **9**), can often be avoided by observing the nonequivalence of nonring protons. Nonequivalence has been observed for protons separated from the chiral center by as many as four carbons (e.g., **6c**).

In each case, the protons that show perceptible nonequivalence exhibit nonequivalence senses consistent with the generalized solvation model **3**–**4**. When the major lactone enantiomer has the configuration depicted in Table I, (*R*)-(−)-**1c** causes R_1 (or H_{endo}) to show high-field nonequivalence. Conversely, R_2 (and H_{exo} and H_γ) show low-field nonequivalence. Except for **5c** and **5d**, the configurations of which we now assign, the absolute configurations of the lactones in Table I are known and have been used to establish the validity of the solvation model.

An additional aspect of the solvation model is that it can assist in making spectral assignments. For example, it was the low-field sense of nonequivalence observed for the high-field α proton of **9** that first suggested that this proton was H_{exo}. Close inspection of coupling constants confirmed this assignment. Similarly, the observation of a high-field sense of nonequivalence for the high-field α-proton resonances of **7** and **8** suggested that these resonances stemmed from endo hydrogens. Apparently the epoxide ring alters the magnetic environment of the α protons so as to change their relative positions[8] with respect to the other lactones. Dioxolanone **10**, derived[9] from (*S*)-(+)-enriched mandelic acid, also shows the utility of the solvation model in making spectral assignments. The NMR spectrum of **10** contains 1 H singlets at δ 5.04, 5.40, and 5.48. The first of these was shown to stem from the hy-

Table I

Lactone		Absolute configuration of major enantiomers R_1	R_2		Nonequivalence amt[b]/sense[3] R_1	R_2	[α]	Enantiomeric excess, %	Ref
 5	a	CH_3	H	(S)	2.0/high		−3.00 (neat)	9	21
	b	CH_3	CH_3CH_2	(R)	1.0/high	4.2/low[e]	+1.31 (c 21.8, $CHCl_3$)	11	22
	c	CH_3	$(CH_3)_2CH$	(S)	2.0/high	4.5 3.5 /low[e]	+1.89 (c 28.5, $CHCl_3$)	21	a
	d	$C_6H_5CH_2$	CH_3	(R)	3.0/high	7.0/low	+1.17 (c 29.1, $CHCl_3$)	9	a
 6	a	CH_3CH_2	H	(R)	3.8/high		−7.65 (c 9.8, EtOH)	72	17
	b	$CH_3CH_2CH_2$	H	(R)	3.8/high		−8.05 (c 5.7, EtOH)	c	17
	c	$CH_3(CH_2)_3$	H	(R)	0.5/high		−7.31 (c 9.7, EtOH)	c	17
 7			H_{endo} 5.0/high		H_{exo} 3.0/low	H_γ 0.5/low		33[d]	18
 8			4.0/high		2.5/low	3.0/low		33[d]	21
 9			~0		1.2/low	7.0/low		33[d]	21
 10			H_b 0.9/high		H_a 3.1/low	H_α 5.0/low		14	9

[a] Absolute configuration assignments based on NMR model reported in this paper. [b] Hertz at 100 MHz. [c] Accurate values of enantiomeric composition not obtainable owing to partial overlap of enantiomeric resonances. [d] Determined by combining known amounts of each pure enantiomer. [e] Values for methyl resonances of R_2.

drogen α to the carbonyl by means of deuterium labeling. It is, however, difficult to determine which of the remaining two singlets arises from H_a and which from H_b. Addition of the shift reagent $Eu(fod)_3$ moves the H_α resonance downfield rapidly but has only a minor nondifferential effect on those of H_a and H_b. In the presence of a severalfold excess of (*R*)-(−)-**1c**, H_α shows the sense of nonequivalence expected on the basis of the solvation model. The sense of nonequivalence of the upfield gemmal hydrogen is the same as that of H_α whereas that of the downfield geminal hydrogen is opposite. Hence, the upfield geminal hydrogen is presumed to be on the same face of the lactone ring as H_α and the assignment in Table I is made accordingly.

Comments on the limitations of the model are in order. Additional basic sites in a lactone (e.g., the epoxide ring in **9**) may interfere with "normal" solvation by chiral **1** as might additional modes of lactone–carbinol interaction. Since knowledge of lactone structure arms one for anticipation of possible "additional interactions", the model should be reliable for assignment of absolute configurations to lactones if intelligently applied.[7] While only γ-lactones are presently described, the model is expected to be applicable to lactones of other ring sizes.[7]

Synthesis, Resolution, and Configurational Assignment of Fluoro Alcohol 1c. Borohydride reduction of trifluoromethyl 9-anthryl ketone (**11**), obtained by high-temperature trifluoroacetylation of anthracene with trifluoroacetic anhydride, yields racemic **1c**. This alcohol is readily resolved via the chromatographic procedure developed[10a] for fluoro alcohol **1b**. For those lacking the automated multigram HPLC system[10b] that makes this resolution routine, we suggest the asymmetric synthesis of (*R*)-(−)-**1c** from **11** using a reagent prepared by Meyers[11] from lithium aluminum hydride and the commercially available (4*S*,5*S*)-(−)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline.[12] While the fluoro alcohol typically obtained by this procedure possesses an optical purity of only 50%, we find that partially resolved **1c** is easily crystallized to enantiomeric purity and that the overall yield of enantiomerically pure (*R*)-(−)-**3** from this acetylation–reduction–crystallization sequence is ca. 25–30%. Even so, the chromatographic resolution of **1c** is more efficient, affording both enantiomers in higher yields.

Resolved fluoro alcohol **1c** is a thermally stable, off-white crystalline solid, stable to dilute acids and bases. If given routine protection from light and oxygen, this fluoro alcohol possesses excellent shelf life. As a consequence of its stability, it can be recovered after use by chromatography on silical gel and/or recrystallization from petroleum ether.

In the presence of (*R*)-(+)-1-(1-naphthyl)ethylamine, the ^1H and ^{19}F NMR spectra of (*S*)-(+)-enriched **1a**,[13] (*S*)-(+)-enriched **1b**,[10,14] and (+)-enriched **1c** show anisochronous resonances for the enantiomeric carbinyl hydrogens and trifluoromethyl groups. Since the three fluoro alcohols show the same senses of nonequivalence, it follows that all are of the same [i.e., (*S*)-(+)] absolute configuration.[14]

When the (+) enantiomers of fluoro alcohols **1a–c** are used as chiral solvating agents for partially resolved solutes such as methyl ethyl sulfoxide,[15,4d] α-methylbenzyl alcohol, α-methylbenzylamine,[4a] or methyl alaninate,[4b] all three induce the same senses of nonequivalence in the NMR spectra of the enantiomeric solutes. Again, this indicates that all three fluoro alcohols have the same absolute configuration, (*S*)-(+).

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. NMR spectra were obtained with Varian Associates A-60A or HA-100 spectrometers. Infrared spectra were obtained with a Beckman IR-12. Optical rotations were determined in a Zeiss visual polarimeter using a 1.0-dm tube. Mass spectra were obtained with a Varian MAT CH-5 instrument. Microanalyses were performed by J. Nemeth and Associates, University of Illinois. For nonequivalence measurements, spectra were determined at 100 MHz and 27 °C using carbon tetrachloride solutions 0.2 M in lactone and 0.6 M in **1c**. Lowering the carbinol: lactone molar ratio or the use of $CDCl_3$ as solvent lessens the nonequivalence, sometimes helpful in reducing signal overlap.

Trifluoromethyl 9-Anthryl Ketone (11). A thick-walled glass tube (or stainless steel bomb) was charged with anthracene (17.8 g, 0.10 mol), trifluoroacetic anhydride (22.0 g, 0.105 mol), and benzene (75 ml), sealed, heated at 200 °C for 15 h, cooled to room temperature, and cautiously opened. The dark reaction mixture was poured onto a column of silica gel (100 g) and eluted with pentane (ca. 1.5 l.). The reddish-orange eluent was concentrated and rechromatographed on silica gel (100 g). Elution with pentane gave a small amount of anthracene followed closely by a long, yellow band of ketone, crude yield 20 g (73%). Recrystallization from methanol gave bright yellow granules: mp 81–84 °C; IR (Nujol) 1750 (C=O), 1200 and 1150 cm^{-1} (CF_3); NMR (CCl_4) δ 7.23–7.95 (m, 8 ArH) and 8.43 (broad, 1 H, ArH at position 10); mass spectrum (70 eV) *m/e* (rel intensity) 274 (M^+, 77.2), 205 (100.0), 177 (79.6), and 176 (44.7).

Anal. Calcd for $C_{16}H_9F_3O$: C, 70.08; H, 3.31; F, 20.78. Found: C, 69.85; H, 3.37; F, 20.42.

2,2,2-Trifluoro-1-(9-anthryl)ethanol (1c). Portionwise addition of excess sodium borohydride (0.25 g, 6.5 mmol) to a stirred methanol solution of **11** (1.5 g, 5.5 mmol) followed by partition between water and methylene chloride and evaporation of the dried (anhydrous $MgSO_4$) organic layer afforded racemic **1c** (1.5 g, 99%): mp 140–142 °C (MeOH–H_2O, 3:1 v/v); NMR (CCl_4) δ 3.42 (d, 1 H, exchangeable OH, J = 5.2 Hz), 6.28 (d of q, 1 H, J_d = 5.2, J_q = 8.0 Hz), 7.15–7.45 (m, 4), 7.62–7.85 (m, 2), 7.6–9.1 (m, very broad, 2, peri H) and 8.20 (s, 1, ArH at position 10); mass spectrum (70 eV) *m/e* (rel intensity) 276 (M^+, 76.5), 207 (100.0), 179 (86.6), and 178 (73.8).

Anal. Calcd for $C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.61; H, 3.91.

Racemic **1c** was resolved by the method of Pirkle and Hoekstra.[10a] Treatment of the high R_f diastereomer with excess methoxide ion in methanol liberated the (+) fluoro alcohol enantiomer which was then chromatographed on silica gel (pentane–benzene, 1:1 v/v) affording (+)-**1c**, mp 142–145 °C, $[\alpha]^{26}D$ 27.2 ± 1.1° (c 6.25, $CHCl_3$).

Asymmetric Reduction of Trifluoromethyl 9-Anthryl Ketone. The procedure of Meyers and Kendall[11] was followed with minor modifications. Thus, in a typical run, a 1-l., three-necked, round-bottom flask fitted with a mechanical stirrer, nitrogen inlet, and low-temperature thermometer and charged with tetrahydrofuran (375 ml), diethyl ether (375 ml), and lithium aluminum hydride (2.4 g, 0.063 mol) was cooled to ca. −20 °C in a well-insulated liquid nitrogen–pentane slush bath. To the stirred reaction mixture was then added solid (4*S*,5*S*)-(−)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline (28.0 g, 0.137 mol) as rapidly as convenient. After a few minutes the reaction mixture was cooled to −75 °C, ketone **11** added (8.2 g, 0.030 mol), and the reaction allowed to warm to −65 °C. After stirring for 3 h at −65 °C, the reaction mixture was allowed to warm to −40 °C and hydrolyzed with aqueous ammonium chloride. The organic layer was collected, washed with water, and extracted with 0.4 N hydrochloric acid (3 × 100 ml) to recover the oxazoline. After separation, the acid layer was promptly poured over NaOH pellets and the oxazoline extracted into ether (2 × 200 ml). After drying, concentration of the ethereal solution followed by cooling to −70 °C afforded recovered crystalline oxazoline, 12.8 g (46%), $[\alpha]^{23}D$ −124.5° (*c* 10.0, $CHCl_3$).

The original organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to afford fluoro alcohol **1c** as a yellow oil, 5.5 g (67%), $[\alpha]^{23}D$ −13.8° (c 6.0, $CHCl_3$) (51% e.e.) after purification by chromatography on silica gel.

Optical Purification of Partially Enriched (−)-1c. A solution of partially resolved (−)-**1c** (11.0 g, ca. 50% e.e.) in high-boiling petroleum ether (700 ml) was concentrated to 500 ml and held at 55 °C. After 12 h, small yellow crystals of essentially racemic alcohol (4.1 g, $[\alpha]^{24}D$ −1.3 ± 1.0°, corresponding to an approximate optical purity of 5%) were collected. In this particular experiment, 2.1 g of large, off-white crystals of enantiomerically enriched alcohol were also collected and quickly separated by hand. Enantiomerically enriched alcohol does not always crystallize at this stage. The mother liquors, concentrated to 300 ml by boiling, deposited a second crop of off-white crystals (1.4 g) upon slow cooling to room temperature. Cooling to 0 °C yielded yet another crop of white crystals that, when combined with crops one and two, amounted to 4.5 g of (−)-**1c** having $[\alpha]^{23}D$ −23.3 ± 1.0° (c 6.0, $CHCl_3$) corresponding to an optical purity of 86%. Subsequent recrystallization of this material afforded optically pure (−)-**1c**, mp 130.5–133 °C.

Enantiomerically Enriched Lactones. Samples of type **6** lactones were generously provided by Meyers and co-workers[17] and lactones **7**, **8**, and **9** were kindly provided by Partridge and co-workers.[18] Type **5** lactones were obtained as described below.

Asymmetric Synthesis of γ-Valerolactone (5a). Ethyl levulinate (5.05 g, 0.035 mol) was reduced by addition to a stirred solution of diisopinocampheylborane[19] [0.05 mol from (−)-α-pinene] in 50 ml of diglyme at 0 °C. Cooling and stirring were maintained for 18 h followed by the addition of 35 ml of 2.5 M NaOH and 16 ml of 30% H_2O_2 and heating to 50 °C for 2 h. The cooled solution was extracted with diethyl ether (3 × 40 ml), acidified with 3 M hydrochloric acid, and the lactone extracted into diethyl ether (5 × 40 ml). After concentration the enantiomerically enriched lactone was purified by preparative GLC (0.375 in. × 25 ft, 5% Carbowax 20M on 60/80 Chromosorb G, 135 °C): NMR (CCl_4) δ 4.56 (m, 1, γ-H), 2.4 (m, 3, α- and β-H), 1.83 (m, 1, α-H), 1.38 (d, 3, J = 6.0 Hz, CH_3).

Asymmetric Synthesis of γ,γ-Dialkyl-γ-butyrolactones (5b–d). Enriched samples of **5b–d** were obtained by the method of Reid and Turner[20] via the low-temperature reaction of Grignard reagents with (−)-menthyl levulinate followed by lactonization. A typical procedure follows. A solution of 5.0 g (19.7 mmol) of (−)-menthyl levulinate in 50 ml of anhydrous ether was cooled to −78 °C. The Grignard reagent (24 mol) in ether (2–3 M) was added dropwise with stirring over a 30-min period. The stirred solution was allowed to warm to −20 °C over 4 h and held at −20 °C for 12 h. The solution was then warmed to 0 °C, 50 ml of Et_2O added, and the solution extracted with dilute H_2SO_4 (3 × 30 ml, 1.5 M). The ether was evaporated and the hydroxy ester hydrolyzed by addition of 50 ml of 3 M NaOH and 40 ml of ethanol with heating to reflux for 2 h. The EtOH was removed by distillation and the aqueous solution washed with CH_2Cl_2 (3 × 30 ml) to remove menthol. Acidification with dilute H_2SO_4 and extraction with CH_2Cl_2 (4 × 30 ml) afforded the hydroxy acid which was lactonized by the azeotropic removal of water with benzene (80 ml). The concentrated lactone solution was diluted with CH_2Cl_2 (80 ml) and washed with 10% $NaHCO_3$ (2 × 10 ml). The dried ($MgSO_4$) CH_2Cl_2 solution was concentrated in vacuo to yield the lactone (40–60%).

Proton Assignments of 5b–d (CCl_4). 5b: δ 2.47 (m, 2, β-H), 2.05 (m, 2, α-H), 1.68 (q, 2, J = 7.5 Hz, CH_2CH_3), 1.36 (s, 3, CH_3CO), 0.98 (t, 3, J = 7.5 Hz, CH_2CH_3). **5c:** δ 2.47 (m, 2, β-H), 1.92 (m, 3, α-H and CH_3CHCH_3), 1.28 (s, 3, CH_3), 1.00 (d, 3, J = 6.5 Hz, CH_3), 0.93 (d, 3, J = 6.5 Hz, CH_3). **5d:** δ 7.17 (m, 5, aromatic), 2.87 (q, 2, J = 14 Hz, benzyl), 2.4–1.7 (m, 4, α-H and β-H), 1.17 (s, 3, CH_3).

Proton Assignments of 7, 8, and 9 (CCl_4). Assignments and coupling constants were sometimes ascertained in separate experiments using Eu(fod)$_3$. **7:** δ 4.87 (m, 1, γ-H), 2.8 (m, 1, β-H), 2.68 (d of d, 1, J_{gem} = 15 Hz, J_{vic} = 10 Hz, H_{exo}), 2.12 (d, 1, J_{gem} = 15 Hz, H_{endo}), 2.2–1.4 (m, 6, $-CH_2CH_2CH_2-$). **8:** δ 5.76 (m, 1, −CH=), 5.54 (m, 1, −CH=), 5.00 (m, 1, γ-H), 3.45 (m, 1, β-H), 2.68 (m, 2, $-CH_2CH{=}CH-$), 2.63 (d of d, 1, J_{gem} = 17.5, J_{vic} = 9.5 Hz, H_{exo}), 2.25 (d of d, 1, J_{gem} = 17.5, J_{vic} = 2.0 Hz, H_{endo}). **9:** δ 4.90 (m, 1, γ-H), 3.54 (m, 2, epoxide ring), 2.92 (m, 1, β-H), 2.60 (m, 2, CH_2CO), 2.47 (d, 1, J_{gem} = 16 Hz, H_{endo}), 2.07 (d of d of d, 1, J_{gem} = 16, J_{vic} = 7.0, J_{HCCCH} = 1.5 Hz, H_{exo}).

Enantiomerically Enriched 5-Phenyl-1,3-dioxolan-4-one (10). A mixture of 2.7 g (17.7 mmol) of (*S*)-(+)-mandelic acid, 6.4 g (42.1 mmol) of racemic mandelic acid, 6.0 g (74.5 mmol) of chloromethyl methyl ether, 9.8 g (150 mmol) of mossy zinc, and 150 ml of diethyl ether was stirred for 7 h, allowed to stand overnight, and washed with water and 10% aqueous $NaHCO_3$. After a final water wash, the organic layer was dried and the ether removed in vacuo, affording crude **10** (4.4 g, 48%), bp 105 °C (0.4 mmHg) [lit.[9] 143 °C (17 mmHg)], which was purified by two recrystallizations from hexane at −20 °C (liquefies on warming to room temperature). The NMR sample studied was a mixture of approximately equal amounts of enriched and racemic dioxolanone having $[\alpha]^{24}D$ 3.6 ± 0.4° (c 10.4, CCl_4), 14 ± 3% optically pure by the NMR method.

In a similar manner, mandelic acid-d_1, obtained via the sodium borodeuteride reduction of benzoylformic acid in dilute Na_2CO_3, afforded 5-phenyl-1,3-dioxolan-4-one-*5-d*: NMR (CCl_4) δ 5.40 (s, 1), 5.48 (s, 1), 7.37 (s, 5).

Acknowledgments. This work has been partially sup-

ported by the National Science Foundation and the National Institutes of Health. We are grateful to R. L. Muntz for the initial preparation[16] of ketone **11**.

Registry No.—(±)-**1c**, 60686-64-8; (+)-**1c**, 60646-30-2; (−)-**1c**, 53531-34-3; **5a**, 19041-15-7; **5b**, 60686-65-9; **5c**, 60646-31-3; **5d**, 60646-32-4; **7**, 43119-29-5; **8**, 43119-28-4; **9**, 59829-44-6; **10**, 60646-33-5; **11**, 784-04-3; anthracene, 120-12-7; trifluoroacetic anhydride, 407-25-0; (4*S*,5*S*)-(−)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline, 51594-33-3; ethyl levulinate, 539-88-8; diisopinocampheylborane, 1091-56-1; (*S*)-(+)-mandelic acid, 17199-29-0; chloromethyl methyl ether, 107-30-2; mandelic acid-d_1, 60646-34-6; 5-phenyl-1,3-dioxolan-4-one-*5-d*, 60646-35-7.

References and Notes

(1) (a) The assignment of absolute configuration of γ-lactones has met with some success by the use of circular dichroism (CD).[1b] Beecham[1c] found a relationship between the sign of the $n-\pi^*$ absorption band and the configuration about the α-carbon atom for a series of γ-lactones. The magnitude and sign of the CD appeared to be independent of ring substitution in other positions. Kuriyama[1d] noted a correlation between chirality at the γ-carbon atom of some α,β-unsaturated γ-lactones and the sign of the $\pi-\pi^*$ Cotton effect. (b) For a brief review see A. F. Beecham, *Tetrahedron Lett.*, 3591 (1968). (c) A. F. Beecham, *ibid.*, 2355 (1968). (d) I. Uchida and K. Kuriyama, *ibid.*, 3761 (1974).

(2) The use of an NMR method giving distinguishable enantiomeric resonances has other inherent advantages over polarimetric methods for determination of enantiomeric composition. For example, for compounds of low specific rotation, typical of lactones of type **5** and **6**, small amounts of optically active impurities can cause errors in polarimetrically determined optical purities with misleading consequences. [For an example see T. Hiyama, T. Mishima, H. Sawada, and H. Nozaki, *J. Am. Chem. Soc.*, **98**, 641 (1976)].

(3) *Sense of nonequivalence* is defined as the field position of a particular signal of the major enantiomer relative to that of the minor enantiomer and is referred to as high field or low field.

(4) Models of the carbinol–substrate interaction causing this nonequivalence have been proposed for (a) aromatic amines, W. H. Pirkle, T. G. Burlingame, and S. D. Beare, *Tetrahedron Lett.*, 5849 (1968); (b) amino esters, W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **91**, 5150 (1969); (c) aryl amine oxides, W. H. Pirkle, R. L. Muntz, and I. C. Paul, *ibid.*, **93**, 2817 (1971); (d) sulfoxides, W. H. Pirkle, S. D. Beare, and R. L. Muntz, *Tetrahedron Lett.*, 2295 (1974); and (e) sulfinates, W. H. Pirkle and M. S. Hoekstra, *J. Am. Chem. Soc.*, **98**, 1832 (1976).

(5) (a) Electron densities at the carbonyl and ring oxygens of **5a** have been calculated[5b] to be 1.482 and 0.893, respectively. Infrared evidence of hydrogen bonding of adenine, uracil derivatives, and *N*-methylacetamide to some γ-lactones at the carbonyl oxygen has been presented.[5c] Furthermore, we find that addition of the shift reagent Eu(fod)$_3$ to carbon tetrachloride solutions of **7** or **8** induces much greater chemical shifts for the protons on the α carbons than for those in the γ position. This indicates coordination of the Eu(fod)$_3$ to the carbonyl oxygen. (b) H. G. Raubenheimer and D. H. DeKock, *J. S. Afr. Chem. Inst.*, **25**, 70 (1972). (c) *ibid.*, **25**, 321 (1972).

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(7) It should be recognized that these chemical shift generalizations are possible for γ-lactones since the latter are relatively planar. These generalizations may not hold for relatively nonplanar lactones even though the fundamental postulates of the model are sound. In such instances, lactone conformation must be considered when determining the relationship between stereochemistry and chemical shift pertubation.

(8) Pertinent NMR studies of the effects of epoxide rings on the chemical shifts of neighboring protons include K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 559 (1964); K. Tori and T. Komeno, *ibid.*, 1157 (1974); D. R. Paulson, F. Y. N. Tang, G. F. Moran, A. S. Murray, B. P. Pelka, and E. M. Vasquez, *J. Org. Chem.*, **40**, 184 (1975); S. G. Davies and G. H. Witham, *J. Chem. Soc., Perkin Trans. 2*, 861 (1975).

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The Facile, Regiospecific Protonation of Alkenes. A Model System

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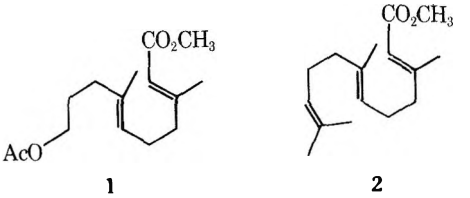
The protonation of olefins generally is accomplished only by relatively strong acids; in contrast, the enzymic protonation of a double bond presumably takes place under much milder conditions. Toward understanding of the mechanisms by which the latter can occur, it is of interest to examine chemical systems in which unusually facile double bond protonation takes place. We report herein such an example which we have uncovered.

To investigate the stability of *E*-α,β-unsaturated methyl esters with respect to double bond isomerization in acidic media,[2] **1** and **2** were treated with 85% phosphoric acid at room

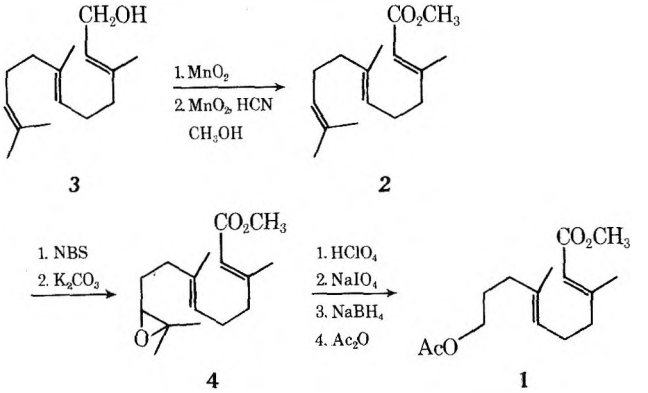


1 **2**

temperature. In contrast to compound **2**, which was recovered unchanged after 30 min, compound **1** underwent rapid and complete transformation. For this study, *E,E*-**1** was prepared stereospecifically, as described below.

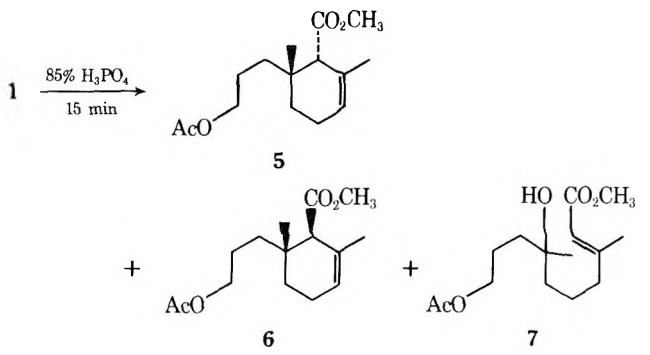
Utilizing active MnO_2 as the oxidant, transformation of (*E,E*)-farnesol (**3**) into **2** was accomplished via the corresponding aldehyde following the two-step procedure developed by Corey.[3] Silica gel chromatography afforded the analytically pure methyl ester with >98% isomeric purity. The ester **2** was then selectively epoxidized to give the known epoxy ester **4** using van Tamelen's NBS reaction, followed by treatment with base.[4] Epoxide **4** was transformed into the desired acetoxy ester **1** by standard means as outlined in Scheme I.

Scheme I



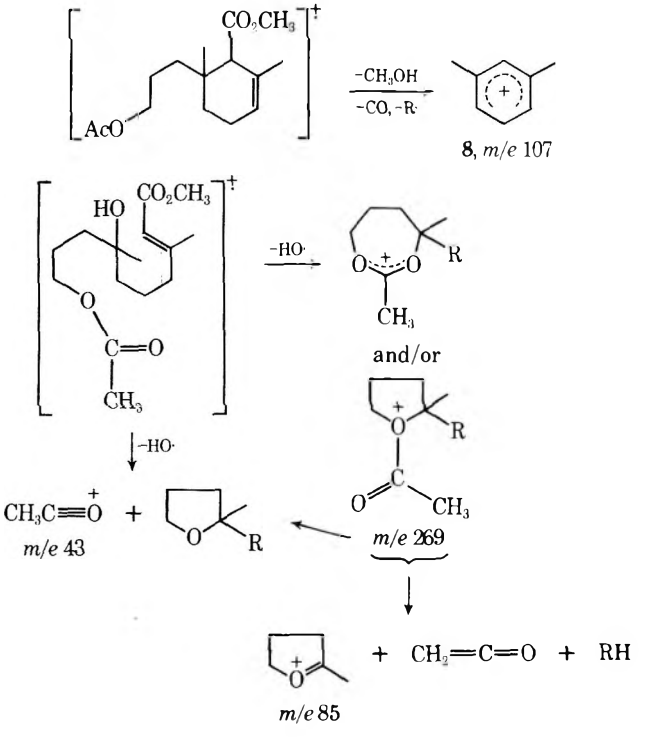
Dissolution of compound **1** for 15 min in 85% phosphoric acid at room temperature resulted in the formation of three major products, as determined by TLC (R_f 0.41, 0.36, 0.04; 5% ethyl acetate in benzene). Separation of these by silica gel chromatography and spectroscopic characterization showed them to be the cyclized epimers **5** and **6** and the acyclic, tertiary alcohol **7** (yields of 45% for **5** and **6** and 38% for **7**). The structural assignments were made on the basis of spectrometric properties. Thus, the NMR spectra of **5** and **6** each show an unsplit methyl at 0.88 ppm, a broadened, vinylic

Scheme II



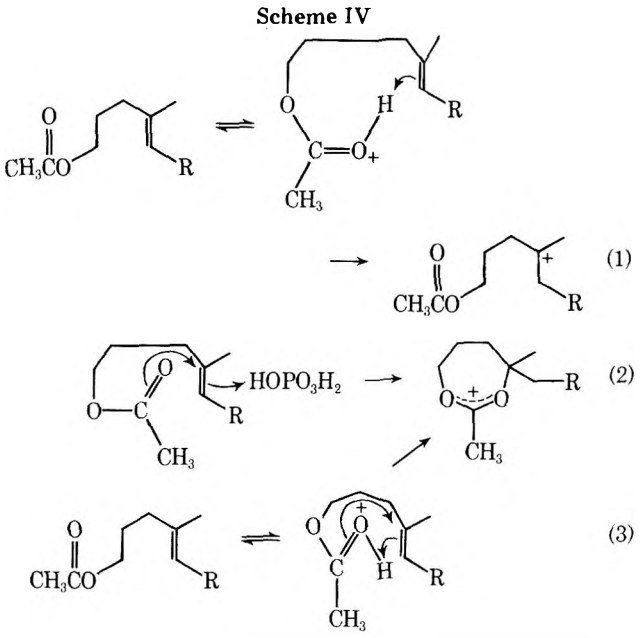
methyl at 1.61 ppm, and only one vinylic proton, as a poorly resolved multiplet at 5.55 ppm, in addition to the other appropriate signals. The mass spectrum of either epimer shows only a small molecular ion, but a base peak at *m/e* 107, formally corresponding to loss of CH_3OH, CO, and the alkyl side chain, forming the highly stabilized carbonium ion **8**. Compound **7** also is easily characterized by its spectral behavior: the IR spectrum shows the hydroxyl group at 3475 cm^{-1}, in addition to the acetate (1740 cm^{-1}) and unchanged α,β-unsaturated ester (1720 and 1650 cm^{-1}); the NMR spectrum, in addition to the signals characteristic of the functionality unchanged from compound **1**, shows an unsplit methyl group at 1.12 ppm and only one vinylic proton (5.63 ppm); finally, the mass spectrum contains no molecular ion, a small peak at *m/e* 269 (M − OH), *no* peak at *m/e* 268 (M − H_2O), a base peak at *m/e* 43 (acetyl), and a characteristic peak at *m/e* 85; these fragments, and lack of a molecular ion, can be rationalized as shown in Scheme III.

Scheme III



In spite of the demonstrated stability of similar olefins, such as **2**, toward direct double bond protonation under these conditions, products **5**, **6**, and **7** all have arisen as the result of rapid, regiospecific protonation of the 6,7 double bond, thereby (formally) forming a carbonium ion at C-7, which then is subject to nucleophilic attack. Additional experiments have provided some evidence regarding plausible causes for this observed selectivity. Thus, when the concentration of compounds **1** and **2** in 85% phosphoric acid is tenfold lower, compound **1** still is protonated exclusively. This suggests that the selectivity is not simply due to solubility differences. Further, no reaction occurs when either compound **1** or **2** is treated with (1) 50% phosphoric acid, (2) glacial acetic acid, or (3) a 30:70 mixture of 85% phosphoric acid and glacial acetic acid. These experiments indicate that the selective protonation of **1** arises from the special, highly ionizing, nonnucleophilic properties[5] of 85% phosphoric acid, probably coupled with some manner of participation by the acetoxy group. Mechanisms for involvement of the acetoxy group which we consider plausible are shown in Scheme IV: (1) intramolecular protonation of the

Scheme IV



double bond by the protonated acetoxy group,[6] (2) stabilization of the carbonium ion (and the transition state leading to it) by the acetoxy carbonyl group, and (3) a combination of these two alternatives, effectively a 1,2 addition to the double bond.[7] Possible underlying mechanistic parallels between this reaction and other examples[8] of chemical, regiospecific protonation of olefins suggest that further study of these systems is warranted.

Experimental Section

Gas chromatographic separations were performed on a 6-ft column packed with 4% OV-101 on high performance Chromosorb G. For TLC and column chromatography, Merck $HF_{254/366}$ and Merck PF_{254} silica gel were used, respectively. Elemental analyses were run by Galbraith Laboratories, Inc.

(*E,E*)-Methyl Farnesate 10,11-Oxide (4).[9] To 314 mg (1.26 mmol) of (*E,E*)-methyl farnesate[10] (**2**) in 16 ml of *tert*-butyl alcohol and 21 ml of H_2O at ca 10 °C was added with stirring under N_2 235 mg (1.32 mmol) of *N*-bromosuccinimide (recrystallized from H_2O). After the reaction mixture was stirred for 80 min without further cooling, most of the solvent was removed under reduced pressure, and the remaining mixture was saturated with NaCl and extracted (3 × 15 ml of diethyl ether). The ether solution was dried ($MgSO_4$), filtered, and concentrated, affording 403 mg of crude bromohydrin **9** as an oil.

To 390 mg (1.12 mmol) of **9** in 15 ml of CH_3OH was added 387 mg of anhydrous K_2CO_3 and the resulting mixture was stirred for 30 min, after which 30 ml of diethyl ether and 30 ml of H_2O were added. The aqueous portion was extracted (3 × 30 ml of pentane), and the combined organic portions were washed (2 × 50 ml of saturated aqueous NaCl), dried ($MgSO_4$), filtered, and concentrated to give 294 mg of crude epoxide. Chromatographic purification (15 g of silica gel, 12% ethyl acetate/hexane) of 284 mg afforded 201 mg of pure epoxide **4** (60%): TLC (20% ethyl acetate/hexane) R_f 0.56; IR (neat) 1720 (C=O) and 1650 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 5.63 (s, 1, $C{=}CHCO_2CH_3$), 5.17 (broad s, 1, C=CH), 3.63 (s, 3, CO_2CH_3), 2.52 (t, 1, J = 6 Hz, OCH), 2.17 (s, $CH_3C{=}CHCO_2$), 1.63 ($CH_3C{=}CH$), and 1.21 and 1.23 ppm [s, 6, $(CH_3)_2C$]; mass spectrum (70 eV) *m/e* (rel

intensity) 266 (1), 123 (56), 109 (30), 102 (48), 95 (30), 83 (31), 81 (36), 73 (33), 70 (40), 69 (100), 59 (53), 57 (38), 43 (35), 31 (54), 29 (38).

(*E,E*)-Methyl 10-Acetoxy-3,7-dimethyl-2,6-decadienoate (1). To 194 mg (0.73 mmol) of epoxide **4** in 15 ml of tetrahydrofuran and 15 ml of H_2O was added with rapid stirring at room temperature 0.15 ml (0.08 mmol) of 3% $HClO_4$. After the reaction mixture was stirred *for 23 h, NaCl was added to saturation, the aqueous portion was ex*tracted (3 × 25 ml of diethyl ether), and the combined organic portions were washed (2 × 15 ml of saturated aqueous NaCl), dried ($MgSO_4$), filtered, and concentrated to give 222 mg of crude glycol (**10**): TLC (50% ethyl acetate/hexane) R_f 0.35; IR (neat) 3425 cm^{-1} (OH); NMR (CCl_4) δ 1.08 ppm [s, 6, $(CH_3)_2COH$]; mass spectrum (70 eV) *m/e* (rel intensity) 284 (6), 81 (63), 59 (52), 43 (100), 41 (56).

To 210 mg (0.74 mmol) of glycol **10** in 10 ml of tetrahydrofuran and 10 ml of H_2O was added 444 mg (2.07 mmol) of $NaIO_4$. After the reaction mixture was stirred for 3 h, NaCl was added to saturation, the layers were separated, the aqueous portion was extracted (1 × 10 ml of pentane, 3 × 10 ml of diethyl ether), and the combined organic portions were washed (2 × 15 ml of H_2O, 1 × 25 ml of saturated aqueous NaCl), dried ($MgSO_4$), and concentrated, affording 158 mg of crude aldehyde (**11**): TLC (20% ethyl acetate/hexane) R_f 0.38; IR *(neat) 2725 cm^{-1} (CHO); NMR (CCl_4) δ 9.77 ppm (s, 1, CHO); mass* spectrum (70 eV) *m/e* (rel intensity) 224 (6), 114 (52), 93 (100), 85 (54), 55 (79).

To 150 mg (0.67 mmol) of aldehyde **11** in 20 ml of CH_3OH was added 14 mg (0.37 mmol) of $NaBH_4$, and the resulting mixture was stirred for 20 min, at which time 1 ml of 2% HCl was added and most of the solvent was removed under reduced pressure. To the remaining mixture was added 25 ml of diethyl ether and 25 ml of H_2O, the layers were separated, the aqueous portion was extracted (3 × 15 ml of diethyl ether), and the combined organic portions were washed (1 × 15 ml of 10% $NaHCO_3$, 2 × 15 ml of saturated aqueous NaCl), dried ($MgSO_4$), and concentrated, affording 149 mg of hydroxy ester (**12**): TLC (20% ethyl acetate/hexane) R_f 0.17; IR (*neat*) 3400 cm^{-1} (OH); NMR (CCl_4) δ 3.51 ppm (t, 2, J = 6 Hz, CH_2OH); mass spectrum (70 eV) *m/e* (rel intensity) 226 (5), 114 (52), 95 (100), 85 (56).

To 146 mg (0.65 mmol) of hydroxy ester 12 in 0.5 ml of pyridine was added 0.5 ml of acetic anhydride, and the resulting mixture was stirred for 23 h, at which time the volatile material was removed under reduced pressure. The remaining oil was dissolved in 25 ml of diethyl ether and the resulting solution was washed (2 × 10 ml of 2% HCl, 1 × 10 ml of 10% $NaHCO_3$, 1 × 10 ml of H_2O, 1 × 10 ml of saturated aqueous NaCl), dried ($MgSO_4$), and concentrated, affording 154 mg of crude acetoxy ester **1**, crude yield 57% based on epoxide **4**. Silica gel chromatography (27 g, 8% ethyl acetate/hexane) of 450 mg of material so obtained provided 335 mg of purified **1**: TLC (20% ethyl acetate/hexane) R_f 0.46; UV max (95% ethanol) 218 nm (ϵ 6700); IR (neat) 1740 (acetate C=O), 1720 (ester C=O), and 1650 cm^{-1} (C=C); NMR (CCl_4) δ 5.64 (s, 1, $CHCO_2CH_3$), 5.14 (broad t, 1, J = 7 Hz, CH=CCH_3), 3.98 (t, 2, J = 6 Hz, $CH_3CO_2CH_2$), 3.64 (s, 3, CO_2CH_3), 2.17 [s, $C(CH_3)$=$CHCO_2CH_3$], 1.99 (s, CH_3CO_2), and 1.64 ppm [s, *C(CH$_3$)=CHCH$_2$]; mass spectrum (70 eV) m/e (rel intensity) 268 (3),* 114 (33), 95 (100). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.86; H, 8.95.

Treatment of (*E,E*)-Methyl 10-Acetoxy-3,7-dimethyl-2,6-decadienoate with 85% H_3PO_4. To 206 mg (0.77 mmol) of acetoxy ester **1** was added 17 ml of 85% H_3PO_4 (Mallinkrodt, AR) and the resulting homogeneous orange solution was stirred for 15 min, at which time 170 ml of H_2O was added. The resulting mixture was extracted (3 × 50 ml of diethyl ether) and 25 ml of saturated aqueous NaCl added to the aqueous portion, which was then extracted again (1 × 50 ml of diethyl ether). The combined organic portions were washed (1 × 50 ml of saturated aqueous $NaHCO_3$, 1 × 50 ml of saturated aqueous NaCl), dried ($MgSO_4$), filtered, and concentrated, affording 195 mg of an oil. Silica gel chromatography (14 g, 2% ethyl acetate/benzene) afforded 81 mg (42%) of purified epimers **5** and **6** *total. Additional elution (ethyl acetate) afforded 71 mg (37%) of* tertiary alcohol **7**.

Epimers **5** and **6** were obtained in three fractions, two (55 and 17 mg) of which each contained only *one* stereoisomer; the middle faction (9 mg) contained a mixture of the two. They are characterized by chromatography: TLC (5% ethyl acetate/hexane) R_f 0.41 (major) and 0.36 (minor) (acetoxy ester **1**, R_f 0.41); GC (100 °C, rising to 200 °C at 6 °C/min) retention times 29.2 min for both epimers and 37.2 min for acetoxy ester **1**. The spectral and analytical behaviors of the two epimers were essentially the same: UV max (95% ethanol) 218 nm (ϵ 5600); IR (neat) 1735 cm^{-1} (ester and acetate C=O); NMR (CCl_4) δ 5.57 (m, 1, C=CH), 3.99 (t, 2, J = 7 Hz, $CH_3CO_2CH_2$), 3.67 (s, 3, CO_2CH_3), 2.63 (s, 1, $CHCO_2CH_3$), 1.99 (s, CH_3CO_2), 1.63 (s, C=CCH_3), and 0.92 ppm (s, 3, CCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 268 (1), 236 (23), 205 (26), 192 (31), 149 (41), 148 (38), 107 (100), 95 (52), 93 (45), 91 (41), 67 (38), 43 (72), 41 (35). Anal Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.33; H, 9.11.

An analytically pure sample of tertiary alcohol **7** was obtained by column chromatography (7 g of silica gel, 20% ethyl acetate/benzene): TLC (25% ethyl acetate/benzene) R_f 0.23; GC (100 °C, rising to 200 *°C at 6 °C/min) retention time 53 min; UV max (95% ethanol) 218 nm* (ϵ 1800); IR (CCl_4) 3475 (OH), 1740 (acetate C=O), 1720 (ester C=O), and 1650 cm^{-1} (C=C); NMR (CCl_4) δ 5.63 (s, 1, C=$CHCO_2$), 4.02 (t, 2, J = 6 Hz, $CH_3CO_2CH_2$), 3.63 (s, 3, CO_2CH_3), 2.13 (d, J = 1 Hz, C=CCH_3), 1.99 (s, CH_3CO_2), and 1.12 ppm (s, 3, $HOCCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 269 (<1), 153 (31), 114 (28), 107 (26), 95 (48), 85 (62), 43 (100). Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.78; H, 9.12.

Determination of Yields of 4-(γ-Acetoxypropyl)-3-carbomethoxy-2,4-dimethylcyclohexenes (5 and 6) and (*E*)-Methyl 10-Acetoxy-7-hydroxy-3,7-dimethyldecenoate (7) by GC. According to the procedure described above, 10.06 mg (0.038 mmol) of acetoxy ester **1** was treated with 0.8 ml of 85% H_3PO_4. After workup the resulting diethyl ether solution was diluted to 25.0 ml and a 1.00-ml aliquot was removed. To the remaining 24 ml was added 2.40 *mg (0.009 mmol) of acetoxy ester 1 as an internal standard. GC* analysis as above showed no remaining acetoxy ester **1** in the reaction mixture. Using compound **1** as an internal standard, the yields of cyclized epimers **5** and **6** were determined to be 45% (ca 3:1 ratio, by TLC) and of tertiary alcohol **7** to be 38%.

Treatment of Methyl Farnesate[11] (2) with 85% Phosphoric Acid. To 2.61 mg (0.0086 mmol) of **2** was added 0.14 ml (2.23 mmol) of 85% H_3PO_4 and the resulting mixture was stirred at room temperature for 30 min, at which time 1.4 ml of water was added. The reaction mixture was extracted (3 × 1 ml of diethyl ether), and 1 ml of saturated aqueous NaCl was added to the aqueous portion, which was then extracted again (1 × 1 ml of diethyl ether). The combined organic portions were washed (2 × 1 ml of saturated aqueous $NaHCO_3$, 1 × 1 ml of saturated aqueous NaCl), dried ($MgSO_4$), and filtered; GC showed unreacted **2** to be the only compound present.

***Treatment of Methyl Farnesate[11] (2) and (E,E)-Methyl 10-*Acetoxy-3,7-dimethyl-2,6-decadienoate (1) with 85% Phosphoric Acid at Tenfold Dilution.** To 2.38 mg (0.0095 mmol) of **2** and 2.24 mg (0.0084 mmol) of **1** was added 2.8 ml (44.54 mmol) of 85% H_3PO_4 and the remaining mixture was stirred at room temperature for 15 min, at which time 28 ml of H_2O was added. The reaction mixture was extracted (3 × 10 ml of diethyl ether) and 10 ml of saturated aqueous NaCl was added to the remaining aqueous portion, which was then extracted again (2 × 10 ml of diethyl ether). The combined organic portions were washed (2 × 10 ml of saturated aqueous $NaHCO_3$, 1 × 10 ml of saturated aqueous NaCl), dried ($MgSO_4$), and filtered; GC showed **2** to be completely unreacted and **1** transformed entirely into **5**, **6**, and **7**.

Treatment of Methyl Farnesate[11] (2) and (*E,E*)-Methyl 10-Acetoxy-3,7-dimethyl-2,6-decadienoate (1) with 50% Phosphoric *Acid. To 2.24 mg (0.0089 mmol) of 2 and* 2.47 mg (0.0092 mmol) of **1 was added 0.49 ml (4.59 mmol) of 50% H_3PO_4 and the resulting mixture was stirred at room temperature for 15 min, at which time 4.9 ml of H_2O was added. The reaction mixture was extracted (4 × 1 ml of diethyl ether), and 1 ml of saturated aqueous NaCl was added to the remaining aqueous portion which was then extracted again (2 × 1 ml of diethyl ether). The combined organic portions were washed (2 × 1 ml of saturated aqueous $NaHCO_3$, 1 × 1 ml of saturated aqueous NaCl), dried ($MgSO_4$), and filtered; GC showed only unreacted **2** and **1** to be present.

Treatment of Methyl Farnesate[11] (2) and (*E,E*)-Methyl 10-Acetoxy-3,7-dimethyl-2,6-decadienoate (1) with Glacial Acetic Acid. To 4.19 mg (0.017 mmol) of **2** and 4.68 mg (0.017 mmol) of **1** was added 2.00 ml (34.86 mmol) of CH_3CO_2H and the resulting mixture was stirred at room temperature for 45 min, at which time 20 ml of *H_2O was added.* The reaction mixture was extracted (3 × 10 ml of diethyl ether), and 10 ml of saturated aqueous NaCl was added to the remaining aqueous portion, which was then extracted again (2 × 10 ml of diethyl ether). The combined organic portions were washed (2 × 10 ml of saturated aqueous $NaHCO_3$, 1 × 10 ml of saturated aqueous NaCl), dried ($MgSO_4$), and filtered; GC showed only unreacted **2** and **1** to be present.

Treatment of Methyl Farnesate[11] (2) and (*E,E*)-Methyl 10-Acetoxy-3,7-dimethyl-2,6-decadienoate (1) with a 30:70 Mixture of 85% Phosphoric Acid and Glacial Acetic Acid. To 1.07 mg (0.0043 mmol) of **2** and 1.23 mg (0.0046 mmol) of **1** was added 0.40 ml (0.0068 mmol) of a 30:70 mixture of 85% H_3PO_4–CH_3CO_2H and the resulting mixture was stirred at room temperature for 1 min, at which time 4 ml of H_2O was added. The reaction mixture was extracted (3

× 1 ml of diethyl ether), and 1 ml of saturated aqueous NaCl was added to the remaining aqueous portion, which was then extracted again (2 × 1 ml of diethyl ether). The combined organic portions were washed (2 × 1 ml of saturated aqueous $NaHCO_3$, 1 × 1 ml of saturated aqueous NaCl), dried ($MgSO_4$), and filtered; GC showed only unreacted **2** and **1** to be present.

Registry No.—**1**, 60718-74-3; **2**, 3675-00-1; **4**, 5299-11-6; **5**, 60718-75-4; **6**, 60718-76-5; **7**, 60718-77-6; **9**, 60718-78-7; **10**, 36999-94-7; **11**, 38227-49-5; **12**, 60718-79-8; *N*-bromosuccinimide, 128-08-5; H_3PO_4, 7664-38-2; acetic acid, 64-19-7.

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(7) The involvement of the more basic (nucleophilic) oxygen of the acetoxy group, as pictured, requires the formation of medium-sized rings; this is consistent with observations made by Gandour (see ref 6). Smaller rings would be required if the other oxygen atom of the acetoxy group is involved; such a possibility cannot be excluded.
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(10) Prepared according to the described[3] procedure and purified by chromatography on silica gel (2% ethyl acetate/hexane); GC analysis (170 °C, 4 °C/min increase, retention time, 15.1 min) indicated greater than 98% isomeric purity.
(11) A mixture (ca. 85:15) of *E,E* and *Z,E* isomers, by GC.

On the Transformation of Benzoin to Tetraphenylfuran in the Presence of *p*-Toluenesulfonic Acid in Boiling Xylene

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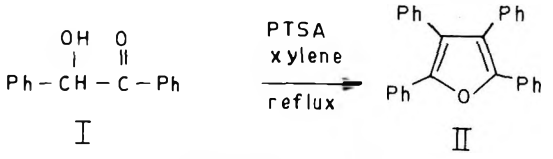
Benzoin (I) is known to undergo an interesting transformation to tetraphenylfuran (II) when refluxed with *p*-toluenesulfonic acid (PTSA) in dry xylene with azeotropic removal of water. This observation, originally made by Berger and Summerbell,[2] is still the best method for making II:[3,4]

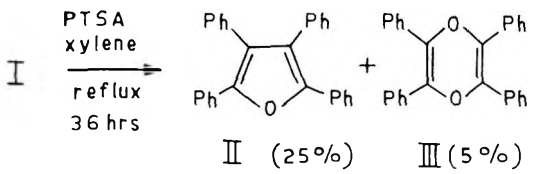


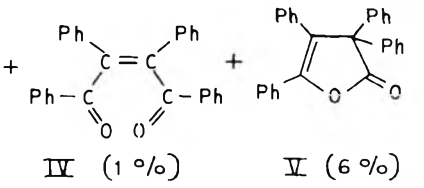
I II

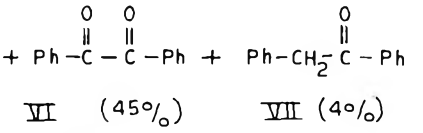
Owing to the simplicity of the reaction and its possible potentiality of opening up of a novel route for the synthesis of furans, the present study was undertaken. In our hands benzoin (I), when refluxed under identical conditions, besides giving II, yielded five more compounds, namely, tetraphenyl-1,4-dioxadiene (III),[2] *cis*-dibenzoylstilbene (IV),[5] tetraphenyllactone (V),[6] benzil (VI),[7] and deoxybenzoin (VII),[8] all of which were identified by comparison with authentic compounds.

Table I. Yields of the Products Obtained in Different Reactions of I (%)

Reaction	II	III	IV	V	VI	VII
1	25.0	5.0	1.0	6.0	45.0	4.0
2	26.0	8.0	2.5	9.0	45.0	5.0
3	30.0	5.0	5.0	9.0	46.0	3.0
4	13.0	3.0	3.0	30.0	23.0	3.0



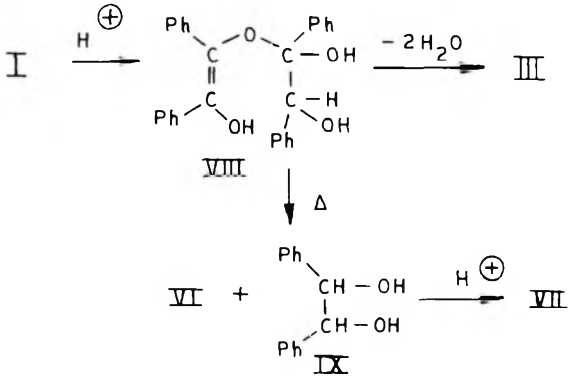




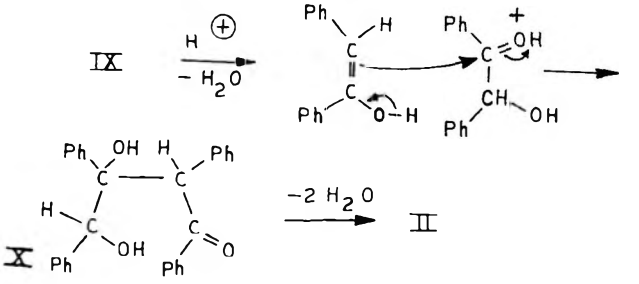
Slightly enhanced yields of all the products were obtained when an equimolar mixture of benzoin and benzoin acetate[9] was refluxed in dry xylene under identical conditions. With deoxybenzoin (VII) added to the reaction mixture yields of the furan (II), *cis*-dibenzoylstilbene (IV), and the lactone (V) increased appreciably.

Similarly when *cis*-dibenzoylstilbene (IV) was added to the reaction mixture the lactone (V) was obtained in higher yields. On the basis of all these observations (Table I) and other related evidences we have rationalized the transformation of benzoin (I) to the observed products in the following manner.

In the presence of acid benzoin (I) undergoes a self-condensation reaction giving rise to the intermediate VIII which then can form III, VI, and VII as follows.

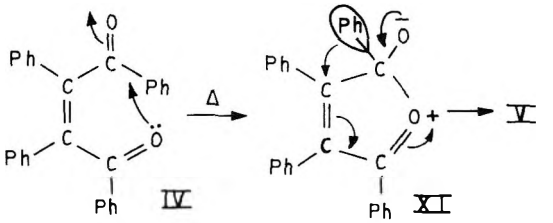


The formation of tetraphenylfuran (II) in this reaction has to involve the condensation of two species forming a carbon–carbon bond and it is quite likely that deoxybenzoin (VII) formed in this reaction condenses with benzoin in the presence of acid to give the intermediate X which could ultimately yield



tetraphenylfuran (II) as given above. This also explains why in the presence of added deoxybenzoin (VII) the furan (II) is formed in higher yield.

The lactone (V) is arising from *cis*-dibenzoylstilbene (IV) through a well-known valence isomerization giving rise to the intermediate XI followed by phenyl migration.[2]



It is not clear how *cis*-dibenzoylstilbene (IV) is formed in this reaction. However, II and III do not yield any detectable amount of IV under the reaction conditions.

Experimental Section[10]

Reflux of Benzoin (I) with *p*-Toluenesulfonic Acid in Dry Xylene (Reaction 1). Benzoin (4.24 g, 20 mmol) and *p*-toluenesulfonic acid (0.1 g) were refluxed in dry xylene (100 ml) with azeotropic removal of water for 36 h. Solvents were removed and the residue was chromatographed over silicic acid. Elution with hexane–benzene (5:1), benzene, and finally with benzene–ethyl acetate (10:1) gave 0.93 g of II (25%), mp 172–174 °C (lit.[2] mp 173.5–175 °C); 0.19 g of III (5%), mp 215–217 °C (lit.[2] mp 214–215 °C); 0.04 g of IV (1%), mp 213–214 °C (lit.[5] mp 212.6–213 °C); 0.23 g of V (6%), mp 137–138 °C (lit.[2] mp 137.1–137.6 °C); 1.89 g of VI (45%), mp 96 °C (lit.[7] mp 94–95 °C); and 0.16 g of VII (4%), mp 56 °C (lit.[8] mp 54–55 °C).

Benzoin (2.12 g, 10 mmol) and benzoin acetate (2.54 g, 10 mmol) (reaction 2), benzoin (4.24 g, 20 mmol) and deoxybenzoin (1.96 g, 10 mmol) (reaction 3), and benzoin (4.24 g, 20 mmol) and *cis*-dibenzoylstilbene (3.88 g, 10 mmol) (reaction 4) were refluxed separately in dry xylene in the presence of *p*-toluenesulfonic acid for 36 h. After the removal of solvents and usual workup products (II–VII) were obtained whose melting points are identical with those of the products obtained in reaction 1 and the yields are given in Table I.

Registry No.—I, 119-53-9; II, 1056-77-5; III, 6963-24-2; IV, 6313-26-4; V, 6963-25-3; VI, 134-81-6; VII, 451-40-1; *p*-toluenesulfonic acid, 104-15-4; benzoin acetate, 574-06-1.

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(10) All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model-137 instrument. The mixture melting points of all the compounds with their authentic compounds did not show any depression. All the compounds gave superimposable IR spectra with those of the respective authentic compounds.

Autocatalysis in the Nitrosation of Dihexylamine

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The kinetics of nitrosation of secondary amines, including catalytic effects, have recently received much attention[1,2] because of the carcinogenic activity of *N*-nitrosamines and their occurrence in the environment. Here we report a novel type of autocatalysis in the nitrosation of dihexylamine.

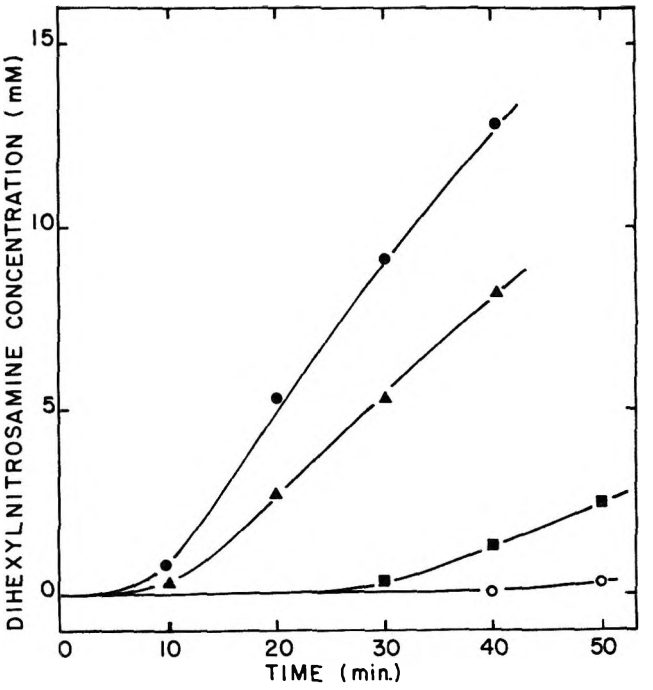

Figure 1. Time course of dihexylnitrosamine formation. Conditions: 20 mM dihexylamine; 30 mM (○), 40 mM (■), 50 mM (▲), and 60 mM (●) nitrite; pH 3.5; 25 °C.

Figure 1 illustrates the time course of dihexylamine nitrosation at four different nitrite concentrations. The initial rates (not shown clearly in Figure 1 because of the expanded ordinate scale) were as expected for the nitrosation of a secondary dialkylamine with a pK_a of 11.01[3] and yielded a second-order rate constant of 0.0004 M^{-2} s^{-1} at pH 3.5.[1] At a particular, well-defined product concentration, however, the rate of the reaction increased abruptly by about 100-fold. At each nitrite concentration, the reaction rate began to increase at a dihexylnitrosamine concentration of 2×10^{-5} M. The reaction rates were proportional to the square of the nitrite concentration in both the initial and catalytic regions of the reaction.

Reaction mixtures, which were initially clear, colorless solutions, became cloudy at the point when the rate began to increase. The point of clouding, determined spectrophotometrically at 500 nm, coincided with a dihexylnitrosamine concentration of 2×10^{-5} M. Surface tension measurements at various times throughout the course of the reaction revealed no abrupt changes of surface tension.

In experiments with dipentyl- and dibutylamine, no autocatalytic effect was observed even when the nitrosation reaction was allowed to proceed almost to completion. Also no cloud point was observed in these reactions. When dihexylamine was mixed with an equimolar concentration of either dipentylamine or dibutylamine, and the resulting solution nitrosated, both amines showed increased rates of nitrosation (Figure 2). The magnitudes of the rate enhancements corresponded to the increasing alkyl chain length of the amine.

In a previous study,[4] we have shown that nitrosation of dihexylamine is strongly catalyzed in the presence of cationic and nonionic surfactants that form micelles in aqueous solution. A similar phenomenon may explain the autocatalytic effect described here for the nitrosation of dihexylamine and the catalytic effect on dipentyl- and dibutylamine nitrosation in the presence of dihexylamine. As the concentration of dihexylnitrosamine exceeds its solubility in aqueous solution, spontaneous emulsification occurs. Hydrophobic interactions lead the amine to concentrate in the dihexylnitrosamine mi-

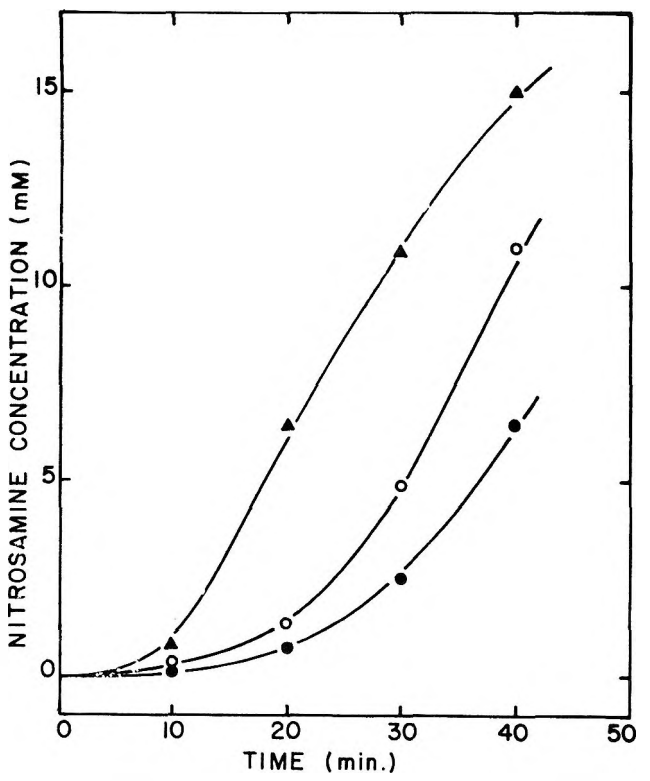

Figure 2. Time course of formation of dipentylnitrosamine (○) and dibutylnitrosamine (●) in the presence of dihexylnitrosamine (▲). Conditions: 20 mM dihexylamine plus 20 mM dipentylamine or 20 mM dibutylamine; 50 mM nitrite; pH 3.5; 25 °C.

crodroplets. Catalysis then occurs in a manner analogous to that observed in the presence of added surfactant.

Experimental Section

Dibutylnitrosamine, dibutylamine, dipentylamine, and dihexylamine were purchased from Eastman Organic Chemicals, Rochester, N.Y. Dihexylnitrosamine was a generous gift from Dr. Harold Röper of the University of Hamburg. Dipentylnitrosamine was synthesized from the parent amine by the method of Druckrey et al.[5] All amines were purified by distillation prior to use; the purity of the nitrosamines was established by gas chromatography.

Kinetic runs were performed in triplicate for each time period in stoppered centrifuge tubes. Reaction mixtures (5-ml volumes) contained 20 mM amine and 20 mM sodium nitrite in citrate–phosphate buffer, pH 3.5 at 25 °C. The buffer was prepared by mixing 0.1 M citric acid with 0.2 M Na_2HPO_4.

Reactions were initiated by adding 3 ml of amine solution; at various times the nitrosation reaction was stopped by adding an excess of solid ammonium sulfamate. After incubation for about 5 min to ensure destruction of nitrite, the contents of the tubes were extracted with an equal volume of methylene chloride and the nitrosamine concentration was determined by a combined gas chromatography–thermal energy analysis system, described by Fine and Roubehler.[6] Chromatography was performed on a 0.125 in. × 10 ft column packed with 5% Carbowax 20M on Chromosorb W. Column temperatures ranged from 155 to 210 °C depending on the nitrosamine investigated. In separate experiments, extraction of all nitrosamines from the aqueous phase into methylene chloride was found to be 98–100% efficient. Surface tension measurements were made with a Fisher surface tensiometer (Fisher Scientific, Pittsburgh, Pa.).

Acknowledgments. This work was supported by Public Health Service Contract N01 CP33315 with the Division of Cancer Cause and Prevention, National Cancer Institute. We are also grateful for support from Hoffmann-La Roche, Inc.

Registry No.—Dihexylnitrosamine, 6949-28-6; dihexylamine, 143-16-8; dipentylnitrosamine, 13256-06-9; dibutylnitrosamine, 924-16-3; dipentylamine, 2050-92-2; dibutylamine, 111-92-2.

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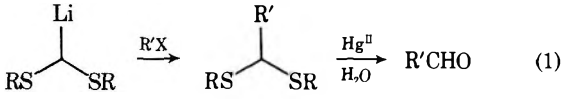
Methylthioformaldine. A New Formaldehyde Anion Equivalent

Summary: Lithium methylthioformaldine, a new formaldehyde anion equivalent, is easily generated and reacts rapidly with primary and secondary halides as well as carbonyl compounds; its hydrolysis to an aldehyde occurs under extremely mild conditions and in high yield.

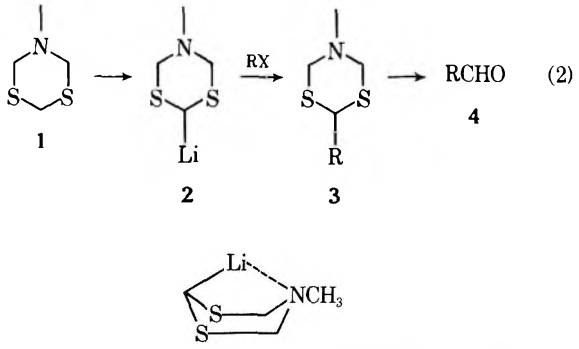
Sir: The alkylation of metalated mercaptal compounds and subsequent hydrolysis of the resulting products has become a standard method of aldehyde synthesis[1] (eq 1). Although



(1)

most reported examples give high yields in both the alkylation and subsequent hydrolysis steps,[1] we have encountered a number of examples in which either or both steps are sluggish. The long reaction times resulted in a number of side reactions which reduced both the yield and purity of the final isolated aldehyde. Frequently tedious chromatographic procedures were required to isolate pure materials.

Speculating that a nitrogen heteroatom in the 5 position of a 1,3-dithiane system might enhance the rate of both the alkylation and hydrolysis steps via intramolecular chelation,[2] we have examined the reactions of several typical alkylating agents with 4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yllithium [lithium methylthioformaldine (LiMTF), **2**][3,4] (eq 2). The



(2)

MTF anion is easily generated in tetrahydrofuran (THF) at −78 °C with 1.05 equiv of *n*-butyllithium. As Table I indicates, the alkylation proceeds quickly between −78 and 0 °C to give high yields of pure dithioacetals **3**. Whereas primary alkyl halides gave no detectable traces of elimination products, moderate amounts of olefin (13–20%) were observed with secondary halides. Unfortunately, the reactions of **2** with mesylates and tosylates gave highly colored mixtures containing only trace amounts of the desired products.[5] In contrast to the more vigorous hydrolysis conditions of the 1,3-dithiane adduct[1] (i.e., 4 h at 50 °C in wet acetonitrile), **3** was easily cleaved[6] in 2 h at room temperature in 90% isolated yield (98% NMR yield) with $HgCl_2$/HgO in wet methylene chloride. In a competitive hydrolysis reaction, a mixture of 1 mmol of 2-pentyl-MTF [**3**, R = $(CH_2)_4CH_3$] and 1 mmol of 2-heptyl-1,3-dithiane was treated with 4 equiv of $HgCl_2$ and 4 equiv of $CdCO_3$ at room temperature in methylene chloride. After 2 h **3** was selectively cleaved to hexanal leaving the 1,3-dithiane untouched. This high reactivity would allow the selective hydrolysis of a specific aldehyde in a multifunctional (i.e., multiprotected) compound. Although there have been methods developed which allow removal of dithianes by mild oxidation,[6] this new group's removal is selective, mild, and totally nonoxidative thus allowing reaction with even the most delicate of compounds. The yield of hydrolysis of the MTF grouping to an aldehyde is considerably higher than for the corresponding 1,3-dithiane (i.e., 90% vs. 65–80%).[6,7]

Table I

Alkylating agent	Alkylation product(s), % yield (mp, °C)[a]	Reaction temp, °C (time, h)
n-Hexyl iodide	Quant	−78 (1)
n-Hexyl bromide	95	−30 (1)
n-Hexyl chloride	40	25 (1)
n-Hexyl mesylate	0	−30 (1)
n-Hexyl tosylate	10	−30 (1)
n-Decyl iodide	95 (37)	−78 (1)
Isopropyl iodide	87	−30 (1)
2-Bromooctane	50	0 (2)
2-Iodooctane	80	0 (2)
Benzaldehyde	quant (113)	−30 (1)
p-Dimethylaminobenzaldehyde	quant (155)	−30 (1)
Butanal	85	−20 (0.5)
Acetophenone	90	−20 (0.5)
4-*tert*-Butylcyclohexanone	85, 3:2 mixture	−20 (1)

[a] Satisfactory analytical and spectral data were obtained for all new compounds.

The extension of this method to a ketone synthesis was unfortunately unsuccessful. When **3** (R = *n*-hexyl or *n*-decyl) was treated in THF with any of the following, no significant amount of metalation was observed (as followed by D_2O quenching): *n*-butyllithium, *n*-butyllithium/HMPA, *sec*-butyllithium, *tert*-butyllithium, lithium diisopropylamide, *n*-butyllithium/TMEDA, or KH. Although this is a drawback for the extensive use of this reagent as a general carbonyl anion, this result does allow for the selective formation of a 1,3-dithiane anion in the presence of a MTF-protected aldehyde.

In a representative aldehyde synthesis hendecanal was produced in 86% overall yield as follows. Freshly sublimed (1 mmHg at 70 °C)[3] **1** [10 mmol (1.34 g)] was dissolved in 20 ml of dry THF (distilled from potassium benzophenone ketyl) under argon. After the solution was cooled to −78 °C, 1.05 equiv of *n*-butyllithium in hexane was added dropwise via syringe. After the mixture was stirred for 1 h, a white precipitate had formed. *n*-Decyl iodide (10 mmol, 2.0 ml, stored over 4 Å molecular sieves and Cu powder) was then added dropwise. The solution was stirred at −78 °C for 1 h and then allowed to warm to 0 °C. Upon reaching 0 °C the solution quickly became homogenous. Water was added and the solution was extracted with ether or methylene chloride. The organic phase was dried over $MgSO_4$, and the solvent removed in vacuo to yield 2.7 g (9.6 mmol, 95% yield) of **3** (R = *n* − $C_{10}H_{21}$) as an oil which crystallized upon standing (mp 37 °C).[8] This material was dissolved in 25 ml of wet methylene chloride under argon and treated with 2.2 equiv of $HgCl_2$ and 2.2 equiv of HgO or $CdCO_3$. The reaction was stirred at room temperature until TLC (silica gel, ether–hexane 1:1) indicated the complete conversion (~2 h) of **3** (R_f 0.6) to the aldehyde **4** (R_f 0.75). Anhydrous $MgSO_4$ was added to aid filtration of the precipitated mercury salts. Water was added to the filtrate and the solution extracted with methylene chloride. After drying over $MgSO_4$, the solvent was removed in vacuo giving 1.5 g of a crude oil. This material was distilled bulb to bulb

giving 1.46 g of pure hendecanal (86% overall yield from the iodide).

Acknowledgment. The authors wish to express appreciation to Jenny Adams and Alice Fukushima for technical assistance.

References and Notes

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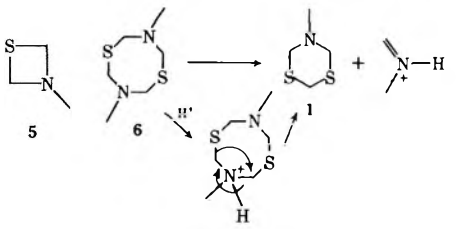
(3) Preparation of **1**: J. Graymore, *J. Chem. Soc.*, 865 (1935); British Patent 943 273 [*Chem. Abstr.*, **60**, 5528a (1964)].
(4) The literature preparation of **1** indicates that cyclobutane **5** is formed by



reaction of formaldehyde, methylamine, and hydrogen sulfide.[3] On close examination by NMR and mass spectroscopy, this intermediate was shown to be cyclooctane **6**. This explains the facile conversion of **6** to **1**.
(5) A. I. Meyers and co-workers have noted similar problems in the alkylation of α-lithio imino esters; cf. *J. Am. Chem. Soc.*, **91**, 763 (1969).
(6) Very low yields of aldehydes were obtained using the following dithiane hydrolysis procedures: refluxing in 20% sulfuric acid [D. Collins and J. Graymore, *J. Chem. Soc.*, 9 (1957)]; Cu(I) triflate [T. Cohen et al., *J. Org. Chem.*, **40**, 812 (1975)]; and CuCl/CuO [K. Narasaka et al., *Bull. Soc. Chem. Jpn.*, **45**, 3724 (1972)].
(7) (a) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971); (b) E. Vedejs and P. L. Fuchs, *ibid.*, **36**, 366 (1971).
(8) Crystalline methiodides of **3** are easily obtained by reaction with a molar excess of clean methyl iodide in peroxide free ether.

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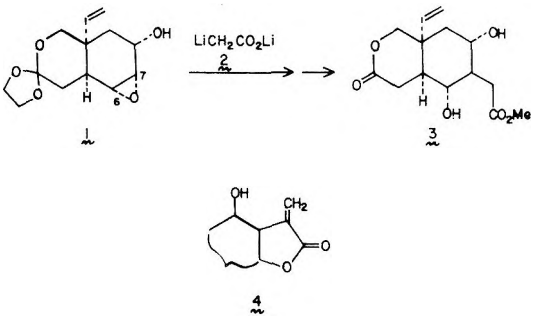
Specific Directing Effects in the Opening of Vicinal Hydroxy Epoxides

Summary: Important directing effects in the ring opening of α-hydroxy epoxides and α-trimethylsilyloxy epoxides are observed in their reactions with dilithioacetate. In reactions of the same substrates with diethylethoxyethynylalane, the key factor determining the sense of ring opening is the stereochemical relationship of the oxy function with the epoxide.

Sir: The decisive step in our recent syntheses of vernolepin and vernomenin involved the reaction of hydroxy epoxide **1** with dilithioacetate (**2**), to give, after suitable treatment, the crucial methyl ester **3**.[1-3] Within the limits of our detection, we were unable to find any product arising from attack at C_6. We thought this result to be surprising since compound **1** would be expected to exist in a preferred conformation, wherein trans diaxial opening would dictate reaction at C_6. We considered the possibility that the ortho ester linkage in **1** effectively shields axial entry at C_6, clearing the way for unencumbered attack at C_7 through a higher energy conformer (Curtin–Hammett principle).[4] Another interesting feature of the process is that the O tetrahydropyranyl derivative of **1** is not attacked by **2**, even under relatively forcing conditions.

In view of the rather wide occurrence of systems such as **4** in both cis- and trans-lactonic arrangements in natural products,[5] many of which have antitumor properties of varying degrees of promise, it was of interest to investigate a potentially straightforward method of synthesis, involving the opening of vicinal, oxygen-substituted epoxides with **2**. Surprisingly, there has been no recorded study, using compound **2**,[6] which is addressed to the attractive possibility of synthesizing systems such as **4** by a direct method of this sort.[7]



As substrates for this investigation, we have studied compounds **5**, **6**, **7**, and **8**. Compound **5** was, of course, well known from the work of Henbest.[8] Silylation of **5** with trimethylchlorosilane–triethylamine–ether at room temperature gives **6** in 81% yield.

The entry to the trans-oxy epoxide series was much facilitated by a recent disclosure of Heathcock, wherein epoxidation of 3-trimethylsilyloxycyclohexene affords **8** as virtually the sole product.[9] Cleavage of **8** with ammonium chloride gives **7**.[9] The reactions of **5**–**8** with **2** are described below.

Lithium diisopropylamide (from 20 mequiv of *n*-butyllithium and an equivalent amount of diisopropylamine) in dimethoxyethane reacted with 10 mequiv of dry acetic acid at −40 °C to generate a solution of **2**. To this solution, was added 1 mequiv of **5**. The system was heated at 55 °C for 15 h. The reaction was quenched with water. After separation of the neutral fraction (starting material) by extraction, the acids were isolated by acidification and extraction. The total acid fraction was heated with *p*-TsOH in benzene and the resultant lactones were readily purified by chromatography on silica gel, using 1:1 ethyl acetate–hexane for elution. There was thus obtained, in 66% combined yield,[10] the homogeneous lactones **9** and **10** in a 3:1 ratio (Scheme I).

When the same reaction was conducted on silyl ether **6**, compounds **9** and **10** were obtained in a ratio of 1:3.2. The structures of the lactones were supported by C and H analysis and infrared and mass spectra: for **9** $\bar{\nu}$ ($CHCl_3$) 1770 cm^{-1}, *m/e* 156 (parent); for **10** $\bar{\nu}$ ($CHCl_3$) 1795 cm^{-1}, *m/e* 156 (parent). Each compound gave a monoacetate (*m/e* 198) with pyridine–acetic anhydride. The NMR spectra ($CHCl_3$) of the two acetates, **9a** and **10a**, readily allowed for their decisive differentiation.[11] In **9a**, both the acetoxy and *O*-lactonic methine protons give rise to a doublet of triplets [δ 3.85 (lactonic methine, J_d = 4.0 Hz, J_t = 11.0 Hz), 4.75 (acetoxymethine J_d = 3.8 Hz, J_t = 11.5 Hz)]. This reflects two virtually equal axial–axial couplings and one axial–equatorial coupling for each proton. Accordingly, the three hydrogens at the asymmetric carbons must be axial—a situation embraced in **9a**. In the isomeric acetoxylactone, the lactonic methine (δ 3.88) is seen as a doublet of doublets (J_1 = 2.8 Hz, J_2 = 11.0 Hz) while the acetoxy-bound methine proton gives rise to a multiplet ($h_{1/2} \sim 7$ Hz). It may be safely concluded that his proton is predominantly equatorially disposed, while the lactonic methine hydrogen is axial. Thus, compounds **9** and **10** both arise from inversion of configuration of the epoxide by anion

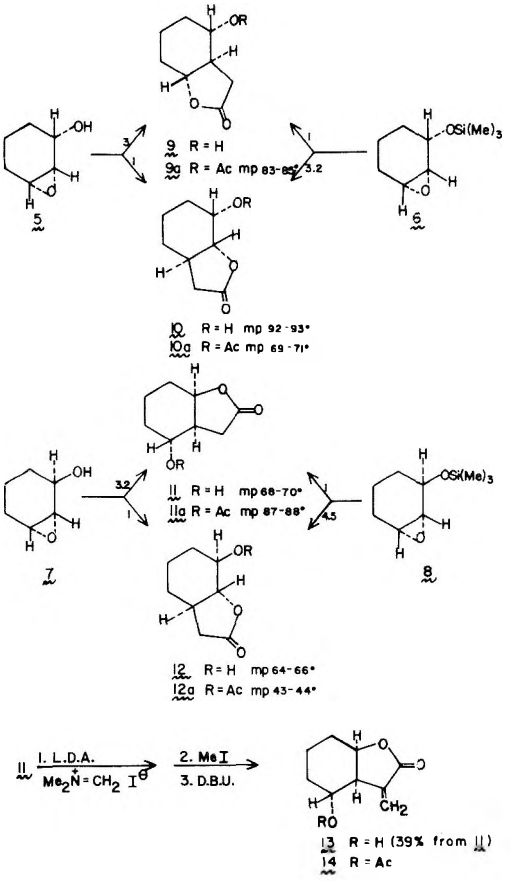
2, but differ in the site of attack and hence the relationship of the hydroxyl and lactonic groups.

Similar reactions were conducted on the trans-hydroxy epoxide **7** and its silyl ether **8**. Compound **7** afforded a 61% yield of a 3.2:1 ratio of homogeneous lactones **11** and **12**, whereas **8** afforded a 50% yield of the same lactones, now in a 1:4.5 ratio. The gross formulae of **11** and **12** were supported by their carbon–hydrogen combustion analyses, in addition to their infrared and mass spectra. The structures of **11** and **12** were, as before, most convincingly established from the NMR spectra of their respective acetylation products, **11a** and **12a**.[11]

In compound **11a**, the lactonic and the acetoxy-bound proton signals overlap, giving a 2 H multiplet centered at δ 4.68 ($H_{1/2}$ 16 Hz). The displacement to lower field, of methine hydrogens bound to the oxygen of a cis-γ-lactone, relative to that found in the corresponding trans system, has been noted in a variety of stereoisomeric γ-lactones.[12] In compound **12a**, the oxygen-bound proton of the trans-fused γ-lactone gives rise to a triplet (J = 10.0 Hz), centered at δ 3.83 ppm, while the acetoxy-bound proton is seen as a doublet of triplets at δ 4.75 (J_d = 5.2 Hz, J_t = 12. 0 Hz). Thus, the two critical methine hydrogens are primarily axial and the stereochemistry is fully defined. Again, compounds **11** and **12** are thus positional isomers, each arising from inversion of configuration in the epoxide opening step.

Structural corroboration was achieved for compound **11**. This compound was converted to its α-methylene derivative, **13**, mp 46–48 °C, without protection of the hydroxyl group, using our new method of α-methylenation.[2] Compound **12**, upon acetylation gave **13**, mp 86–87 °C. The 270-MHz NMR spectrum of **13**, thus produced, was identical with that of authentic sample (mp 87–88 °C) previously prepared by Ziegler and associates by their elegant solvolysis reaction.[13a]

Scheme I. Reactions of α-Oxygenated Epoxides with Dilithioacetate



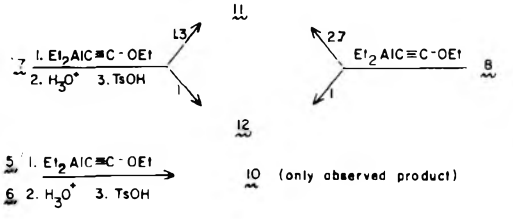
The major products in the cases of silyl ether **6** and hydroxy epoxide **7** may be rationalized in terms of trans-diaxial opening of a conformer in which the bulky substituents are disposed equatorially. However, such an analysis leads to formulations contrary to observation in the cases of **5** and **8**, and is apparently of little predictive value. What emerges from these dianion reactions is that the stereochemistry of the epoxide relative to the adjacent oxygen is not of decisive influence. The key factor seems to be the nature of the α oxygen. When this is originally hydroxyl, the nearest bond of the epoxide is displaced. When this is an trimethylsilyl ether, the remote epoxide bond is preferentially severed.

Recently we have developed a mild method for the conversion of cyclohexane oxides into trans-fused γ-lactones using diethylethoxyalkynylalane.[13b] It was therefore of interest to determine the course of this reaction in the presence of neighboring oxygen functionality. Toward this end, we studied the opening of epoxides **5**–**8** with the alane reagent. Reactions were conducted in toluene, from −40 °C to room temperature as previously described. For purposes of analysis, the resultant trans ethoxyalkynylcarbinols were directly converted to the corresponding ethyl esters by treatment with aqueous HCl–THF.[13b] These suffered lactonization with *p*-TsOH–benzene under reflux for 16 h. The results are shown in Scheme II. The yields of the final lactones were in the range of 50 to 60%.

It will be noted that the reaction course in the alane opening depends largely on the stereochemical relationship of the oxy function and the epoxide, and only to an insignificant extent on whether the oxygen is initially in the form of a hydroxyl or a trimethylsilyl ether. *These results are opposite to those in the dianion case, wherein the nature of the oxygen, rather than its stereochemical relationship with the epoxide, appears to be decisive.*

The openings of **5** and **6** by the alane reagent may be interpreted in terms of trans-diaxial opening of the epoxide, assuming a preferred equatorial conformation of the neighboring oxygen substituent. In these cases, the alane is not reacting under a directing influence by the neighboring oxygen, since attack occurs trans to the oxygen. The reaction course in the case of **7** and **8** may be interpreted in terms of competing forces. Attack nearest the oxygen would be favored on conformational (trans diaxial) considerations, while remote attack would possibly be favored on the grounds of steric hindrance. There is no clear evidence for a directing influence from the proximate oxygen, though this can not be ruled out.

Scheme II. Reactions of α-Oxygenated Epoxides with Diethylalkoxyethynylalane



In the dianion reactions, it would appear that the neighboring hydroxyl, now undoubtedly present as an alkoxide, provides a guidance for ring opening at the adjacent epoxide center in both the cis and trans series. This may well be the consequence of energy lowering solvation possibilities between the metal alkoxide and the attacking dianion.

It should be emphasized that, although the ability of a hydroxyl group to participate in, and direct, the course of epoxide openings has been documented in some recent studies,[14–16] these pertain only to the free hydroxyl which is cis to

the epoxide. The specificity in the case of **2**[17] undoubtedly involves the alkoxide, rather than the free alcohol, and is operative in both the cis and trans series. A pertinent analogy is seen in the work of Fried, wherein a remote hydroxyl (presumably as the alkoxide) is efficacious in directing epoxide opening by an organoalane.[18,19] In the cases studied here (**7** and **8**), one can not clearly discern such an effect, though it may be operative as one of several competing forces.

There emerges from our data an empirically based approach for the construction of variations of system **4** with complete stereospecificity and acceptable regioselectivity by utilization of suitable organometallic equivalents of $^{-}CH_2CO_2H$. The feasibility of using this methodology in total synthesis contexts is receiving continuing attention.

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(4) See E. Eliel, "The Stereochemistry of Carbon Compounds", McGraw Hill, New York, N.Y., London, 1962. That the ground-state conformation of **1** is the one in which the hydroxyl and vinyl are equatorial to the B ring was strongly suggested by high field NMR analysis of its derived acetate; see ref 1, footnote 18.
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(8) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957). NMR spectral analysis indicated that starting materials **5** and **7** were uncontaminated with one another.
(9) C. G. Chavdarian and C. H. Heathcock, *Synth. Commun.*, **6**, 277 (1976). We thank Professor Heathcock for apprising us of his excellent method prior to its publication.
(10) in our experience, the yields of epoxide openings using the Creger method[6] do not exceed 70% even with very simple substrates. The virtue of the method is that the reagent is quite stable to temperatures up to 60–70 °C where this becomes necessary. However, for reasons not yet understood, substantial starting material is recovered even with copious excesses of reagent and long reaction times.
(11) NMR analysis of the parent alcohols gives the same conclusions. However, in the three compounds which have trans-fused γ-lactones, the carbinol methine proton signal overlaps with that arising from the oxygen-bound lactonic methine.
(12) This trend has been noted in a variety of cis- and trans-fused γ-lactones with and without α-hydroxyl groups. The oxygen-bound lactonic methine proton absorbs in the region δ 4.6–5.0 ppm while that of the trans series absorbs in the region 3.8–4.1 ppm. This is the case in seven sets of isomers which we have prepared.
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(17) In the case of compound **1** the total regiospecificity must involve factors in addition to alkoxy participation. The shielding effect of the axial bond of the ortho ester would appear to be a reasonable explanation. This would account for the failure of **1** tetrahydropyranyl ether to react at all, since the expected mode, based on compound **6**, would occur at carbon **6**. For a possibly related case, in the synthesis of luciduline, see W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.*, **94**, 4780 (1972).
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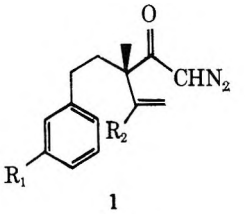
β,γ-Unsaturated Diazo Ketones. A New Initiator for Polyolefinic Cationic Cyclization

Summary: The synthetic utility of β,γ-unsaturated diazo ketones as initiators for polyolefinic cationic cyclization is described.

Sir: Recently, we have demonstrated that β,γ-unsaturated diazo ketones are synthetically useful precursors of both simple and annulated cyclopentenone derivatives when subjected to acid-catalyzed decomposition.[1] We now wish to report that such species hold considerable potential for the initiation of polyolefinic cyclizations.[2] To our knowledge unsaturated diazo ketones have not previously been employed in this manner.[3]

In order to investigate this question, we selected diazo ketones **1a–c** which would not be expected to become involved



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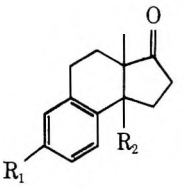

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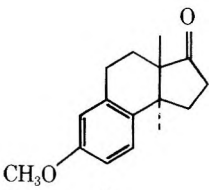


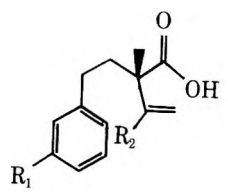
3

a, $R_1 = OCH_3$; $R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = H$; $R_2 = H$
d, $R_1 = OH$; $R_2 = CH_3$

in complex structural rearrangements. In addition, diazo ketone **1a** appeared ideally suited for our initial study since two of the four possible tricyclic products (**2a** and **3**) have recently been prepared and their stereochemistry established rigorously by Jeger and co-workers.[4]

The required diazo ketones **1a–c** were prepared in the usual manner (oxalyl chloride, CH_2N_2) from the corresponding β,γ-unsaturated acid derivatives **4a–c**[5] readily available via alkylation of the ethyl esters of either 2,3,3-trimethylacrylic acid or tiglic acid with the tosylate ester of phenethyl or *m*-methoxyphenethyl alcohol, employing as base the lithium diisopropylamide–hexamethylphosphoramide complex in THF described recently by Rathke[6] and Schlessinger.[7] Subsequent hydrolyses of the resultant esters (5% aqueous NaOH, 14 h) yielded **4a**[5] and **4b**[5] as crystalline solids (mp 73.5–74.5 °C and 67–68 °C, respectively), whereas **4c**[5] was obtained as a viscous oil. The overall yields based on the tosylate were 43–48%.

After examination of a variety of Lewis acid and complementary solvent systems, it was determined that 1.1 equivalent of BF_3-Et_2O in freshly distilled nitromethane at room temperature for 0.5 h constituted the optimal conditions[8] to effect the desired cyclizations. In that event diazo ketone **1a** yielded two tricyclic products, **2a** and **5a**,[5] accompanied by a small amount of **6a**[5] (31, 12, and 10% yield, respectively).[9] Interestingly, when methylene chloride was employed as solvent, a small amount (2%) of **8**[5,10] was formed in addition to **2a**, **5a**, and **6a**. Similar cyclizations (BF_3-Et_2O/CH_3NO_2; 0.5 h) of **1b** yielded **2b**,[5] **6b**,[5] and **7**[5] (46, 10, and ~2% yield,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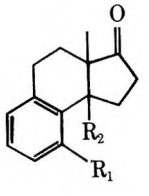
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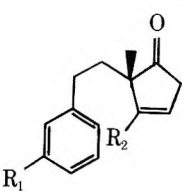
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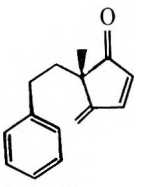
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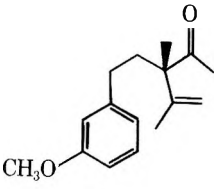
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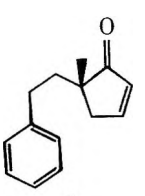
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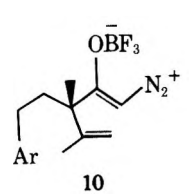
respectively) while **1c** gave only **9**[5] in 21% yield. Finally, treatment of **6b** under the above conditions led to its complete recovery. The above structures were deduced from the spectroscopic properties, after resolution of the product mixtures via a combination of separation techniques including VPC on 6% Carbowax 20M and HPLC on SIL-X-1 (CH_2Cl_2:hexane, 3:2). Confirmation of structure **2a** was obtained by comparison of the IR and NMR spectra with those obtained originally by Jeger.[11]

Drieding molecular model studies of diazo ketones **1a–c** indicated that the most favorable conformation for cyclization would lead to a cis C/D ring fusion. This result is due primarily to the tetrahedral geometry of the α-carbon center. That in fact the cyclization in each case proceded stereospecifically to yield the cis-fused tricyclic ketones **2a, 2b,** and **5a** followed initially from a comparison of their 220-MHz NMR spectra. Second, ketone **5a** and the previously known **2a** were individually transformed to **2b** employing a demethylation–dehydroxylation reaction sequence. To this end, cleavage[12] of the phenolic methyl esters with BBr_3 led to phenols **2d**[5] and **5d,** which were transformed to the corresponding diethyl phosphate ester with diethyl chlorophosphate. Subsequent reduction with excess potassium in liquid ammonia, employing ether as a co-solvent according to the method of Rossi and Bunnett,[13] gave in both cases a single tricyclic ketone which was identical in all respects (e.g., IR, 220 MHz NMR, and retention properties) with **2b.**

A reasonable reaction pathway for the above cyclizations involves initial complexation by BF_3 with the oxygen of the diazo ketone functionality to yield intermediate **10;** subsequent loss of nitrogen and cyclization then leads in the case of **1a** and **1b** to a tertiary carbocation (**11**).[14] The exact nature of this initial cyclization is currently unknown but at least two alternatives exist. The initial loss of nitrogen could preceed σ-bond formation, and/or the π system of the β,γ-olefinic bond could participate directly in nitrogen loss. The resultant tertiary carbocation is, in most instances, sufficiently long lived to suffer capture by the π system of the aromatic ring before the cation can be removed from the reaction coordinate by proton loss. Support for the stepwise nature of this sequence arises from the BF_3-catalyzed decomposition of **1c** which yields cyclopentenone **9** as the major product. In this case the initial cyclization leads to a less stable, short-lived secondary carbocation (**12**) which rapidly losses a proton before capture by the aromatic system can take place.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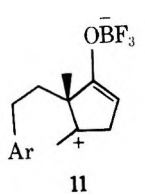
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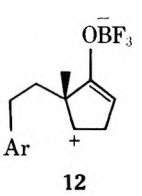
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The synthetic utility of this approach to polycyclic ketones is readily apparent when one considers alternative approaches to such tricyclic systems. For example **2a** was prepared by Jeger in eighteen steps from dehydroabietic acid.[4] Studies are continuing in our laboratory to extend the synthetic use of acid-catalyzed decomposition of unsaturated diazo ketones.

Acknowledgment. We are glad to acknowledge the generous support of this investigation by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by Research Corporation.

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(4) v. T. Wirthlin, H. Wehrli, and O. Jeger, *Helv. Chim. Acta*, **57**, 351 (1974).
(5) This new compound gave satisfactory spectroscopic properties (IR and 220-MHz NMR) as well as elemental analysis and/or exact mass of the molecular ion by high resolution mass spectroscopy.
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(7) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).
(8) Similar conditions were employed by L. N. Mander and co-workers; see ref 3.
(9) Yields were determined by calibrated VPC measurements and are based on converted starting material. Isolated yields were ~5–7.5% lower.
(10) An authentic sample of ketone **8** was prepared from acid **4a** by treatment with 2 equiv of CH_3Li: M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).
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(13) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 2314 (1973).
(14) Alternatively, BF_3 complexation could take place at the diazo carbon atom. Subsequent cyclization via nucleophilic displacement of N_2 by the π system would then lead to a tertiary carbonium ion from which the various products arise.

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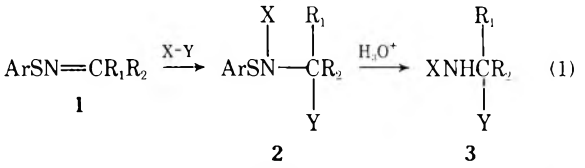
Synthesis of Secondary and Tertiary Carbinamines from N-Alkylidenearenesulfenamides and Alkyl- and Aryllithium Reagents

Summary: A one-step synthesis of secondary and tertiary carbinamines from *N*-alkylidenearenesulfenamides **1** and alkyl and aryllithium reagents is described which illustrates the synthetic value of **1** as "masked" imine derivatives of ammonia.

Sir: The importance of the imine (azomethine) group in organic synthesis is well documented.[1] Its use, however, is generally restricted to N-substituted imines since imines of ammonia (>C=NH) are easily hydrolyzed and undergo self-condensation reactions.[1a,b] *N*-Alkylidenearenesulfenamides[2] **1** may potentially act as "masked" imine derivatives of ammonia. Addition of a reagent X–Y to the C–N double bond in **1** would yield a sulfenamide **2**,[3] and the relatively weak S–N

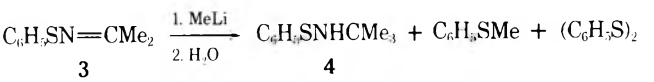


(1)

bond in **2** may be cleaved to yield the free amine derivative (eq 1). *N*-Alkylidenearenesulfenamides **1** are considerably more resistent to hydrolysis than imines, can be stored indefinitely at 10–20 °C, and are conveniently prepared in good yield from disulfides, aldehydes or ketones, silver nitrate, and ammonia.[2]

Current methods for preparing primary amines include the Gabriel synthesis and the Leuckart, Hofmann, Curtius, and Schmidt reactions.[4] Many of these procedures are inconvenient, often hazardous, and limited to specific classes of compounds. The reductive amination of ketones with sodium cyanoborohydride gives good yields of secondary carbinamines, but fails with hindered and diaryl ketones.[5] The Ritter reaction is the only convenient method for preparing tertiary carbinamines, but generally requires the presences of strong acids.[6]

We wish to report a convenient "one-step" synthesis of secondary and tertiary carbinamines from **1** and alkyl- and aryllithium reagents using the reaction sequence described in eq 1. Reaction of methyllithium with *N*-isopropylidenebenzenesulfenamide **3**[2] gave, after hydrolysis, sulfenamide **4**[7]



(78%), thioanisole (~1%), and diphenyl disulfide (~2%). Maximum yields of **4** were obtained when 2 equiv of methyllithium were added to **3** and the mixture was allowed to stand for 1.5 hr at room temperature and then refluxed for 0.5 hr. Lower temperatures and the addition of TMEDA reduced the yield of **4**.[8]

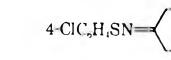
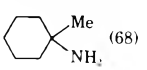
The amine may be isolated in "one step" from **1** and the alkyl- or aryllithium reagent; the procedure is illustrated for the synthesis of 2-phenyl-2-aminopropane (Table I, entry 7).

In a 500-ml, 3-necked flask equipped with magnetic stir bar and nitrogen and syringe inlets were placed 10 mmol of isopropylidenebenzenesulfenamide (**3**) in 100 ml of dry ether. Phenyllithium (20 mmol) was added via syringe with cooling. After stirring for 1 hr at room temperature and for 0.5 hr at reflux, the reaction mixture was cautiously hydrolyzed with 100 ml of water. The two-phase mixture was separated and the organic phase washed with 6 N HCl (3 × 10 ml). The acid solution was removed under vacuum to yield the crude, solid amine hydrochloride. The amine hydrochloride was treated with 20 ml of 20% sodium hydroxide solution and the free amine extracted into ether (3 × 20 ml). After drying over $MgSO_4$ removal of solvent gave 0.8 g (61%) of an oil, bp 70–73 °C (8 mm) [lit.[9] 72–73 °C (8 mm)], identified as 2-phenyl-2-aminopropane. The amine obtained by this procedure prior to distillation was 96% pure as indicated by NMR and GLC.

Using this procedure the synthesis of secondary and tertiary carbinamines from **1** and alkyl- and aryllithium reagents is summarized in Table I. Amines obtained by this method were essentially pure (>97%), as indicated by NMR, GLC, and TLC, and were identified by comparison of their properties with literature values. As Table I indicates, this method for amine synthesis gave good yields of amines even with *tert*-butyllithium (entries 4 and 8). In general, yields of amines using this "one-step" procedure were better and in many cases more convenient than the multistep methods reported in the literature (Table I).

The one-step preparation of amines from **1** and alkyl- and aryllithium reagents represents a new and convenient synthesis of hindered secondary and tertiary carbinamines from a novel substrate. Overall, the reaction (eq 1) results in the conversion of a carbonyl group to a secondary or tertiary carbinamine and demonstrates the potential synthetic utility

Table I. Synthesis of Amines from *N*-Alkylidenearenesulfenamides **1**

Entry	Sulfenamide[a] [bp, °C (mm), % yield]	Lithium reagent[b]	Amine (% yield)[c]	Ref
1	$C_6H_5SN{=}CHC_6H_5$ [70%][d]	MeLi	$C_6H_5C(Me)HNH_2$ (79)	*e*
2		*n*-BuLi	$C_6H_5C(CH_2CH_2CH_2CH_3)HNH_2$ (70)	*f*
3		C_6H_5Li	$(C_6H_5)_2CHNH_2$ (59)	*g*
4		Me_3CLi	$C_6H_5C(CMe_3)HNH_2$ (87)	*h*
5	$C_6H_5SN{=}CHMe$ [64–65 (0.04), 52]	C_6H_5Li	$C_6H_5C(Me)HNH_2$ (61)	*e*
6	$C_6H_5SN{=}CMe_2$	*n*-BuLi	$CH_3CH_2CH_2CH_2C(NH_2)(Me)_2$ (57)	*i*
7		C_6H_5Li	$C_6H_5C(NH_2)(Me)_2$ (61)	*j*
8		Me_3CLi	$Me_3CC(NH_2)(Me)_2$ (43)	*k*
9	$C_6H_5SN{=}C(Me)CH_2CH_3$ [73 (0.1), 97]	C_6H_5Li	$C_6H_5C(Me)(CH_2CH_3)NH_2$ (83)	*l*
10	$4\text{-}ClC_6H_4SN{=}CMeC_6H_5$ [58–60, 62]	MeLi	$C_6H_5C(NH_2)Me_2$ (59)	*j*
11	 [141 (0.15), 45]	MeLi	 (68)	*m*

[a] Reference 2 unless otherwise noted. [b] Aldrich Chemical Co. [c] Isolated yields; reactions run at least twice and yields averaged. [d] See also F. A. Davis, J. M. Kaminski, E. W. Kluger, and H. S. Freilich, *J. Am. Chem. Soc.*, **97**, 7085 (1975). [e] Reference 5. [f] A. de Roocker and P. de Radzitsky, *Bull. Soc. Chim. Belg.*, **82**, 195 (1963); *Chem. Abstr.*, **59**, 9845h (1963). [g] J. Kalaman and B. Ryban, *Chem. Zvesti*, **20**, 79 (1966); *Chem. Abstr.*, **64**, 17453e (1966). [h] H. Christol, A. Lavrent, and M. Mousseron, *Bull. Chem. Soc. Fr.*, 2319 (1961); *Chem. Abstr.*, **56**, 14133 (1962). [i] *Zh. Obshch. Khim.*, **29**, 174 (1959); *Chem. Abstr.*, **53**, 21661h (1959). [j] Reference 6. [k] J. W. Timberlake, M. L. Hodges, and K. Betterton, *Synthesis*, 633 (1972). [l] D. J. Cram, C. A. Kingsburg, and A. Langemann, *ibid.*, **81**, 5785 (1959). [m] P. Kovacic and S. S. Chaudhary, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 35.

of *N*-alkylidenearenesulfenamides as "masked" imine derivatives of ammonia.

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(8) Products were analyzed by gas chromatography on a 6-ft 6% OV-17 on 60/80 mesh Chromosorb W (regular) column by comparison of peak areas with standard solutions of reaction products. Analysis were performed at least twice and the results averaged. With 2 equiv of MeLi at −78 °C for 4 h, **3** gave 48% **3** and 50% **4**. With 2 equiv each of MeLi and TMEDA at 25 °C, **3** gave 38% **3** and 58% **4**.
(9) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3929 (1949).

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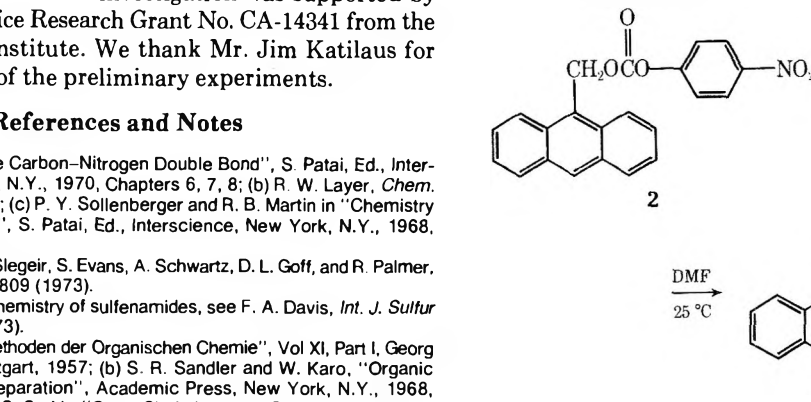
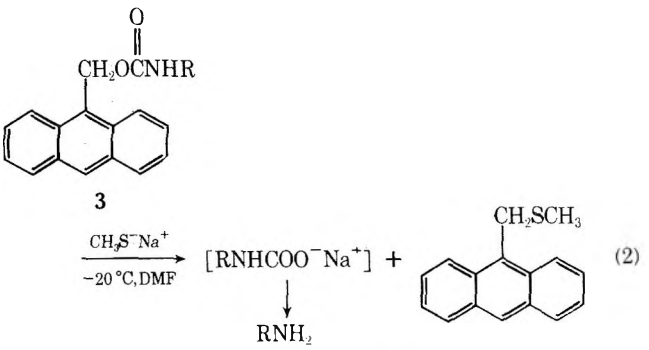
A New Method for Protecting Amines

Summary: A new method for protecting amines which hinges on the unusual chemical properties of the 9-anthrylmethyl system is described.

Sir: The 9-anthrylmethyl system **1** provides an excellent blocking group for carboxylic acids, phenols and thiophenols.[1] We now describe a simple procedure for protecting amines[2] which is based on their conversion to 9-anthrylmethyl carbamates **3**. Such carbamates are readily produced at room temperature by treating the amine with 9-anthrylmethyl *p*-nitrophenyl carbonate **2** (eq 1).[3]



Deblocking does not rely on the carbamate function but, rather, on a special property of the 9-anthrylmethyl system. What is invoked is a new type of substitution at a saturated carbon atom attached to the 9 position of the anthracene nucleus; these reactions are noteworthy for the speed with which they occur under mild conditions.[1,4] Removal of the protective group is achieved by treating the 9-anthrylmethyl carbamate with the sodium salt of methyl mercaptan (eq 2).



At −20 °C the reaction requires from 1 to 7 h; at 25 °C it is complete in <4 min. The results obtained with a wide variety of carbamates are summarized in Table I; the yields refer to pure, isolated amines.

Despite the ease with which these compounds are deblocked by the sodium salt of methyl mercaptan they are resistant to the action of various bases and acids. Thus, the 9-anthrylmethyl carbamates derived from *n*-octylamine, di-*n*-octylamine, and *p*-phenetidine are unaffected by exposure for 24 h to 30 mol of anhydrous ethylamine in DMF at 25 °C. They are also unaffected by 2 equiv of lithium hydroxide (0.01 N) in aqueous dioxane after 6 h at 25 °C. These carbamates are also stable to 4 equiv of sulfuric acid (0.10 N) in aqueous dioxane for 1 h at 25 °C, and they are not affected by 10 equiv of trifluoroacetic acid (1.0 M) in dioxane after 1 h at 25 °C.

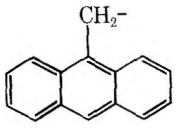


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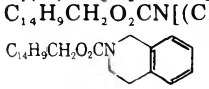
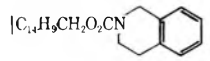
Table I. The Deblocking of 9-Anthrylmethyl Carbamates By The Sodium Salt of Methyl Mercaptan[a,b]

9-Anthrylmethyl carbamate (3)	Amine	% yield	Reaction time, hr
$C_{14}H_9CH_2O_2CNH(CH_2)_7CH_3$	*n*-Octylamine	77	7
$C_{14}H_9CH_2O_2CNH(CH_2)_2C_6H_4Cl$	2-(*p*-Chlorophenyl)ethylamine	86	*c*
$C_{14}H_9CH_2O_2CNHCH_2C_6H_4Cl$	*p*-Chlorobenzylamine	82	1
$C_{14}H_9CH_2O_2CNHCH(C_6H_5)_2$	Benzhydrylamine	97	5
$C_{14}H_9CH_2O_2CNHC_6H_4OC_2H_5$	*p*-Phenetidine	91	3
$C_{14}H_9CH_2O_2CN[(CH_2)_7CH_3]_2$	Di-*n*-octylamine	85	c
	Tetrahydroisoquinoline	86	2

[a] In DMF under N_2 0.3 M in carbamate and 0.6 M in CH_3SNa; at −20 °C unless otherwise stated. [b] Satisfactory elemental analyses and NMR and IR spectra were obtained for all new compounds. [c] 4 min at 25 °C.

Table II. 9-Anthrylmethyl Carbamates Deblocked by CF_3CO_2H in CH_2Cl_2[a]

9-Anthrylmethyl carbamate (3)	Amine	% yield[b]
$C_{14}H_9CH_2O_2CNHCH(C_6H_5)_2$	Benzhydrylamine	95
$C_{14}H_9CH_2O_2CNHCH(CO_2CH_3)CH_2C_6H_5$	Phenylalanine methyl ester	92
$C_{14}H_9CH_2O_2CNHCH_2C_6H_4Cl$	*p*-Chlorobenzylamine	88
	Tetrahydroisoquinoline	90

[a] 5 min at 0 °C; 0.1 M in carbamate, 1.0 M in CF_3CO_2H. [b] Pure isolated amine.

In contrast, the protective group is removed by a methylene chloride solution of trifluoroacetic acid. Thus, while the 9-anthrylmethyl carbamate derived from benzyhydrylamine is not affected by treatment for 12 h with 10 equiv of trifluoroacetic acid (1.0 M) in dioxane at 25 °C, it is completely deblocked in 5 min by 10 equiv of trifluoroacetic acid (1.0 M) in methylene chloride at 0 °C and a 95% yield of the pure amine is isolated. As can be seen from Table II this is a general phenomenon and it provides a valuable alternative deblocking procedure.

A typical example of the blocking procedure follows. To a stirred suspension of 7.46 g (20.0 mmol) of **2**[3] in 40 ml of DMF was added 2.43 ml (20.0 mmol, 2.84 g) of *p*-chlorobenzylamine. After 45 min the reaction mixture was poured into ice–water and extracted with methylene chloride. The aqueous phase was then extracted with benzene and the combined organic layers were washed with 10% hydrochloric acid, 10% sodium carbonate, and, finally, water. Drying and removing solvents yielded 7.0 g of needles, mp 167–171 °C, which on recrystallization from benzene–hexane gave 5.996 g (86% yield) of analytically pure pale yellow needles, mp 180–181 °C.

Deblocking is illustrated by the following example. A 200-ml flask containing 1.855 g (5 mmol) of 9-anthrylmethyl *p*-ethoxyphenylcarbamate and 0.701 g (10 mmol) of the sodium salt of methyl mercaptan was sealed with a rubber stopple, immersed in a bath at −20 °C, and dry N_2 was passed in for ~20 min. Then 50 ml of cooled, deoxygenated DMF was added via syringe and the resulting solution was stirred at −20 °C under N_2; the reaction was monitored by TLC [silica gel plates, hexane–ethyl acetate (2:1), short and long UV]. After 3 h the blue fluorescence of the carbamate was gone; the reaction mixture was then poured into a mixture of 100 ml of ice and 200 ml of 10% HCl and extracted with 200 ml of benzene–diethyl ether (1:1) and then with 100 ml of benzene. The resulting aqueous acid solution was rendered alkaline with 20% NaOH and extracted twice with diethyl ether and once with benzene. The organic phase was washed with water and dried ($MgSO_4$), and the solvents were removed. This gave 0.620 g (91% yield) of *p*-phenetidine which was 99+% pure by VPC and whose NMR spectrum was identical with that of an authentic sample. From the benzene–diethyl ether extract of the original acid solution 1.214 g (100% yield) of essentially pure 9-anthrylmethyl sulfide, mp 110–112 °C, was isolated.

Acknowledgment. We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

(1) N. Kornblum and A. Scott, *J. Am. Chem. Soc.*, **96**, 590 (1974).
(2) For a recent review of this subject, see L. A. Carpino, *Acc. Chem. Res.*, **6**, 191 (1973).
(3) The synthesis of the requisite carbamates was initially attempted via the chloroformate obtained on treating 9-hydroxymethylanthracene with 1 mol of phosgene, but this chloroformate proved to be rather unstable, readily breaking down to give 9-chloromethylanthracene and carbon dioxide. 9-Anthrylmethyl *p*-nitrophenyl carbonate **2** is easily obtained by treating 9-hydroxymethylanthracene with 1.5 mol of *p*-nitrophenyl chloroformate (Aldrich's 97% material purified by sublimation) in THF in the presence of 1.5 mol of pyridine. Recrystallization of the crude product from benzene gives analytically pure **2** (~85–90% yield), mp 108–109 °C dec.
(4) C. W. Jaeger and N. Kornblum, *J. Am. Chem. Soc.*, **94**, 2545 (1972).

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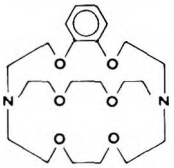

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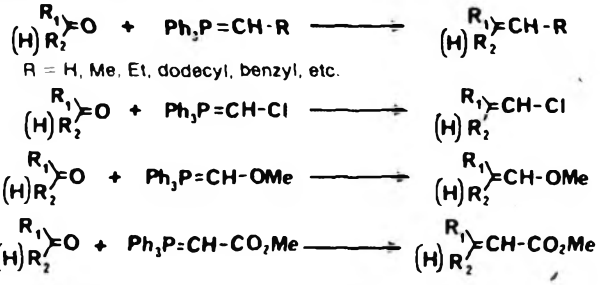
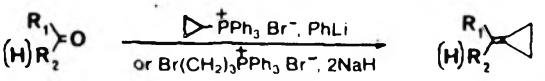
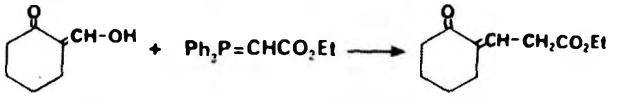


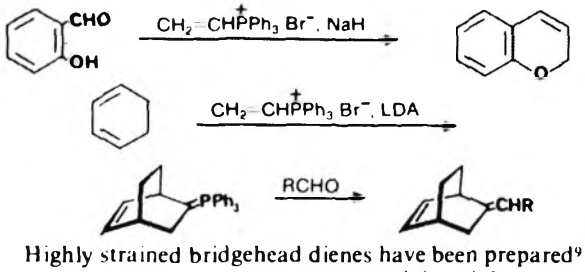
Cyclopropyltriphenylphosphonium bromide or (3-bromopropyl)triphenylphosphonium bromide react with carbonyl compounds in the presence of a base to yield the corresponding cyclopropylidene derivatives.[5]



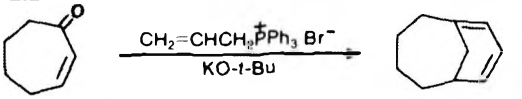
Reaction of α-hydroxymethylene ketones with (carbethoxymethylene)triphenylphosphorane gives α-methylene-substituted ketones.[6]



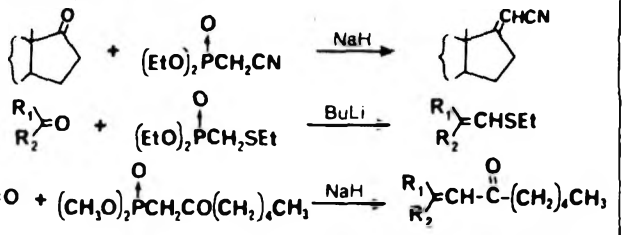
Schweizer's Reagent, vinyltriphenylphosphonium bromide, has been used in the synthesis of a variety of heterocyclic compounds.[7] It has also been employed as a dienophile and the resulting cycloadduct used as a Wittig reagent.[8]



Highly strained bridgehead dienes have been prepared[9] from α,β-unsaturated ketones and allyltriphenylphosphorane *via* a Michael-type addition followed by an intramolecular Wittig reaction.



The ylides derived from alkoxyphosphonates have been used for the same type of olefination as the phosphoranes. Representative reactions of diethyl (cyanomethyl)phosphonate,[10] diethyl (ethylthiomethyl)phosphonate[11] and dimethyl (2-oxoheptyl)phosphonate (used in prostaglandin synthesis) are as follows:



A partial list of our wide spectrum of phosphoranes, phosphonates, phosphonium halides and some of their deuterated analogs is shown below.

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3) A. Maercker, *Org. React.*, 14, 270 (1965).
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7) E.E. Schweizer, J. Liehr, and D.J. Monaco, *J. Org. Chem.*, 33, 2416 (1968) and references cited therein.
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11) E.J. Corey and J.I. Shulman, *ibid.*, 35, 777 (1970).

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C510-6	(Carbethoxymethylene)triphenylphosphorane	25g $13.50 100g $36.00
C5762-6	(Chloromethyl)triphenylphosphonium chloride	25g $18.10
15,731-7	Cyclopropyltriphenylphosphonium bromide	5g $9.00 25g $29.75
D9170-5	Diethyl (cyanomethyl)phosphonate	10g $15.00; 50g $59.00
15,653-1	Diethyl (ethylthiomethyl)phosphonate	5g $17.75; 25g $59.15
15,793-7	Dimethyl (2-oxoheptyl)phosphonate	10g $21.65; 50g $72.20
13,007-9	Methyltriphenylphosphonium bromide	25g $5.00 100g $13.40
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